U.S. Department of Health and Human Services
National Institutes of Health
National Institute of Allergy and Infectious Diseases (NIAID)

RFP-NIH-NIAID-DAIT-08-10
Statistical & Data Coordinating Center

OMB Control Number 0990-0115

1. **OFFERORS ARE RESPONSIBLE FOR ROUTINELY CHECKING THE FOLLOWING WEBSITE FOR ANY SOLICITATION AMENDMENTS. NO ADDITIONAL NOTIFICATION OF ANY AMENDMENTS WILL BE PROVIDED BY THIS OFFICE.** http://www.fedbizopps.gov/

2. **SECTION A – SOLICITATION/CONTRACT FORM -- PURCHASE AUTHORITY: FAR 1.602-1**
NOTE: The issuance of this solicitation does not commit the government to an award.

3. **Issue Date:**	4. **Due Date:**	5. **Small Bus. Set-Aside:**
07/20/2007	November 7, 2007 **Time:** 4:00PM Local Time Bethesda, MD	[ ]Yes [x] No **8(a) Set-Aside:** [ ]Yes [x] No **NAICS #:** 541710 (See Part IV, Section L.)

6. **Just In Time:**	7. **Number of Awards:**	8. **Technical Proposal Page Limits:**
[x] No [ ] Yes (See Part IV, Section L.)	[x] Only 1 Award [ ] Multiple Awards	See Section J, Attachment 1, Packaging and Delivery of Proposal

9. **Issued By:**	[x] **NIAID reserves the right to make awards without discussion.**	
Donald E. Collie Contracting Officer Office of Acquisitions, NIAID, NIH 6700-B Rockledge Drive Room 3214, MSC 7612 Bethesda, MD 20892-7612	10. **Options:** **[ ] No** **[x] Yes** (See Part IV, Section L.)	11. **Period of Performance:** **7/31/2008-7/30/2014 (Base Period)** **7/31/2014-7/30/2015 (with Option)**

12. **Primary Point of Contact:**	13. **Secondary Point of Contact:**	14. **Protest Officer:**
Name : Deborah Blyveis **Phone:** 301-594-7211 **Fax:** 301-480-4675 **E-Mail:** blyveisd@niaid.nih.gov	**Name:** Donald E. Collie **Phone:** 301-496-0992 **Fax:** 301-480-4675 **E-Mail:** dcollie@niaid.nih.gov	See Section L.1., Paragraph j. Service of Protest.

15. **COLLECT CALLS WILL NOT BE ACCEPTED. FACSIMILE SUBMISSIONS ARE NOT ACCEPTABLE.**

16. Offers will be valid for 120 days unless a different period is specified by the Offeror on the form entitled "Proposal Summary and Data Record, NIH-2043" (See Attachment 13, Proposal Summary and Data Record, NIH, 2043)

17. **Offeror must be registered in the Central Contractor Registry (CCR) prior to award of a contract. (http://www.ccr.gov)**

18. **DELIVERY ADDRESS INFORMATION**

19. **Hand Delivery or Overnight Service:**	20. **U.S. Postal Service or an Express Delivery Service**
Deborah Blyveis Office of Acquisitions, NIAID, NIH 6700-B Rockledge Drive, Room 3214 Bethesda, MD 20817	Deborah Blyveis Office of Acquisitions, NIAID, NIH 6700-B Rockledge Drive, Room 3214, MSC 7612 Bethesda, MD 20892-7612

21. The **Official Point of Receipt** for the purpose of determining timely delivery is the address provided in Block 19, above. The original paper copy with original signatures is the official copy for recording timely receipt. If the original paper copy of your proposal is not received by the Contracting Officer or Designee at the place and time specified, then it will be considered late and handled in accordance with FAR 15.208 entitled " Submission, Modification, Revision, and Withdrawal of Proposals." FACSIMILE SUBMISSION OF PROPOSALS IS NOT ACCEPTABLE.

DETAILED TABLE OF RFP CONTENTS

PART I - THE SCHEDULE

THE CONTRACT SCHEDULE SET FORTH IN **SECTIONS B THROUGH H**, HEREIN, CONTAINS CONTRACTUAL INFORMATION PERTINENT TO THIS SOLICITATION. IT IS **NOT** AN EXACT REPRESENTATION OF THE CONTRACT DOCUMENT THAT WILL BE AWARDED AS A RESULT OF THIS SOLICITATION. THE CONTRACT COST OR PRICE AND OTHER CONTRACTUAL PROVISIONS PERTINENT TO THE OFFEROR *(i.e., those relating to the organizational structure [e.g., Non-Profit, Commercial] and specific cost authorizations unique to the Offeror's proposal and requiring Contracting Officer Prior Approval)* WILL BE DISCUSSED IN THE NEGOTIATION PROCESS AND WILL BE INCLUDED IN THE RESULTANT CONTRACT. THE ENCLOSED CONTRACT SCHEDULE IS INTENDED TO PROVIDE THE OFFEROR WITH THE NECESSARY INFORMATION TO UNDERSTAND THE TERMS AND CONDITIONS OF THE RESULTANT CONTRACT.

SECTION B - SUPPLIES OR SERVICES AND PRICES/COSTS

ARTICLE B.1. BRIEF DESCRIPTION OF SUPPLIES OR SERVICES

This contract provides for the establishment and management of a Statistical and Data Coordinating Center to support the National Institute of Allergy And Infectious Diseases sponsored clinical research programs in allergy/asthma, autoimmune, and transplant-related diseases.

ARTICLE B.2. ESTIMATED COST AND FIXED FEE

a. The estimated cost of the Base Period of this contract is $ TBD.

b. The fixed fee for the Base Period of this contract is $ TBD. The fixed fee shall be paid in installments based on the percentage of completion of work, as determined by the Contracting Officer. Payment shall be subject to the withholding provisions of the clauses ALLOWABLE COST AND PAYMENT and FIXED FEE referenced in the General Clause Listing in Part II, ARTICLE I.1. of this contract. Payment of fixed fee shall not be made in less than monthly increments.

c. The total estimated amount of the contract, represented by the sum of the estimated cost plus the fixed fee for the Base Period of this contract is $ TBD.

d. If the Government exercises its option pursuant to the OPTION PROVISION Article in SECTION H of this contract, the Government's total estimated contract amount represented by the sum of the estimated cost plus the fixed fee will be increased as follows:

	Estimated Cost ($)	**Fixed Fee ($)**	**Estimated Cost Plus Fixed Fee ($)**
Base Period Option Period(s): Total [Base Period and Option(s)]	TBD	TBD	TBD

e. Total funds currently available for payment and allotted to this contract are $ TBD of which $ TBD represents the estimated costs, and of which $ TBD represents the fixed fee. For further provisions on funding, see the LIMITATION OF FUNDS clause referenced in Part II, ARTICLE I.2. Authorized Substitutions of Clauses.

f. It is estimated that the amount currently allotted will cover performance of the contract through TBD.

g. The Contracting Officer may allot additional funds to the contract without the concurrence of the Contractor.

ARTICLE B.3. PROVISIONS APPLICABLE TO DIRECT COSTS

This article will prohibit or restrict the use of contract funds, unless otherwise approved by the Contracting Officer. The following is a list of items that may be included in the resultant contract as applicable. 1) Acquisition, by purchase or lease, of any interest in real property; 2) Special rearrangement or alteration of facilities; 3) Purchase or lease of any item of general purpose office furniture or office equipment regardless of dollar value; 4) Travel Costs; 5) Consultant Costs; 6) Subcontract Costs; 7) Patient Care Costs; 8) Accountable Government Property; and 9) Research Funding.

ARTICLE B.4. ADVANCE UNDERSTANDINGS

Specific elements of cost, which normally require prior written approval of the Contracting Officer before incurrence of the cost (e.g., foreign travel, consultant fees, subcontracts) will be included in this Article if the Contracting Officer has granted his/her approval prior to contract award.

SECTION C - DESCRIPTION/SPECIFICATIONS/WORK STATEMENT

ARTICLE C.1. STATEMENT OF WORK

a. Independently and not as an agent of the Government, the Contractor shall be required to furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government, as needed to perform the Statement of Work, dated June 20, 2007, attached hereto and made a part of this Solicitation (See SECTION J - List of Attachments).

ARTICLE C.2. REPORTING REQUIREMENTS

All reports required herein shall be submitted in electronic format. In addition, one (1) hardcopy of each report shall be submitted to the Contracting Officer and the Project Officer, unless otherwise specified.

a. Technical Progress Reports

1. In addition to the required reports set forth elsewhere in this Schedule, the preparation and submission of regularly recurring Technical Progress Reports will be required in any contract resulting from this solicitation. These reports will require descriptive information about the activities undertaken during the reporting period and will require information about planned activities for future reporting periods. The frequency and specific content of these reports will be determined prior to contract award. Please refer to the "Reporting Requirements and Deliverables" in SECTION J. List of Attachments.

   For proposal preparation purposes only, it is estimated that in addition to the required electronic version(s), 2 hard copies of these reports will be required as follows:

   ( ) Monthly
   ( ) Quarterly
   (X) Semi-Annually
   ( ) Annually
   (X) Annually (with a requirement for a Draft Annual Report)
   ( ) Final - Upon final completion of the contract
   (X) Final - Upon final completion of the contract (with a requirement for a Draft Final Report)

2. Summary of Salient Results

   The Contractor will be required to prepare and submit, with the final report, a summary (not to exceed 200 words) of salient results achieved during the performance of the contract. This report will be required on or before the expiration date of the contract.

b. Other Reports/Deliverables

1. **Source Code and Object Code**

Unless otherwise specified herein, the Contractor shall deliver to the Government, upon the expiration date of the contract, all source code and object code developed, modified, and/or enhanced under this contract.

ARTICLE C.3. INVENTION REPORTING REQUIREMENT

All reports and documentation required by FAR Clause 52.227-11 including, but not limited to, the invention disclosure report, the confirmatory license, and the government support certification, shall be directed to the Extramural Inventions and Technology Resources Branch, OPERA, NIH, 6705 Rockledge Drive, Room 1040-A, MSC 7980, Bethesda, Maryland 20892-7980 (Telephone: 301-435-1986). In addition, one copy of an annual utilization report, and a copy of the final invention statement, shall be submitted to the Contracting Officer. The final invention statement (see FAR 27.303(a)(2)(ii)) shall be submitted to the Contracting Officer on the expiration date of the contract.

The annual utilization report shall be submitted in accordance with the DELIVERIES Article in SECTION F of this contract.

If no invention is disclosed or no activity has occurred on a previously disclosed invention during the applicable reporting period, a negative report shall be submitted to the Contracting Officer at the address listed above.

To assist contractors in complying with invention reporting requirements of the clause, the NIH has developed "Interagency Edison," an electronic invention reporting system. Use of Interagency Edison is encouraged as it streamlines the reporting process and greatly reduces paperwork. Access to the system is through a secure interactive Web site to ensure that all information submitted is protected. Interagency Edison and information relating to the capabilities of the system can be obtained from the Web (http://www.iedison.gov), or by contacting the Extramural Inventions and Technology Resources Branch, OPERA, NIH.

SECTION D - PACKAGING, MARKING AND SHIPPING

All deliverables required under this contract shall be packaged, marked and shipped in accordance with Government specifications. At a minimum, all deliverables shall be marked with the contract number and contractor name. The Contractor shall guarantee that all required materials shall be delivered in immediate usable and acceptable condition.

SECTION E - INSPECTION AND ACCEPTANCE

a. The Contracting Officer or the duly authorized representative will perform inspection and acceptance of materials and services to be provided.

b. For the purpose of this SECTION, the Project Officer in Article G.1 is the authorized representative of the Contracting Officer.

c. Inspection and acceptance will be performed at, 6610 Rockledge Drive, Bethesda, Maryland 20892.

Acceptance may be presumed unless otherwise indicated in writing by the Contracting Officer or the duly authorized representative within 30 days of receipt.

d. This contract incorporates the following clause by reference, with the same force and effect as if it were given

in full text. Upon request, the Contracting Officer will make its full text available.

FAR Clause **52.246-9, Inspection of Research and Development (Short Form)** (April 1984).

SECTION F - DELIVERIES OR PERFORMANCE

ARTICLE F.1. PERIOD OF PERFORMANCE

a. The period of performance of this contract shall be from July 31, 2008 through July 30, 2014.

b. If the Government exercises its Option 1 pursuant to the OPTION PROVISION Article in Section H of this contract, the period of performance will be increased by one additional year.

ARTICLE F.2. DELIVERIES

Satisfactory performance of the final contract shall be deemed to occur upon performance of the work described in the
STATEMENT OF WORK Article in SECTION C of this contract and upon delivery and acceptance by the Contracting Officer, or the duly authorized representative, of the following items in accordance with the stated delivery schedule, See Attachment 3, “Reporting Requirements and Deliverables” in SECTION J. List of Attachments.

a. The items specified below as described in the REPORTING REQUIREMENTS Article in SECTION C of this contract will be required to be delivered F.o.b. Destination as set forth in FAR 52.247-35, F.o.b. DESTINATION, WITHIN CONSIGNEES PREMISES (APRIL 1984), and in accordance with and by the date(s) specified below and any specifications stated in SECTION D, PACKAGING, MARKING AND SHIPPING, of this contract.

ARTICLE F.3. CLAUSES INCORPORATED BY REFERENCE, FAR 52.252-2 (FEBRUARY 1998)

This contract incorporates the following clause(s) by reference, with the same force and effect as if it were given in full text. Upon request, the Contracting Officer will make its full text available. Also, the full text of a clause may be accessed electronically at this address: http://www.acquisition.gov/comp/far/index.html.

FEDERAL ACQUISITION REGULATION (48 CFR CHAPTER 1) CLAUSE:

52.242-15, Stop Work Order (August 1989) with **Alternate I** (April 1984).

SECTION G - CONTRACT ADMINISTRATION DATA

ARTICLE G.1. PROJECT OFFICER

The following Project Officer(s) will represent the Government for the purpose of this contract:

[To be specified prior to award]

The Project Officer is responsible for: (1) monitoring the Contractor's technical progress, including the surveillance and assessment of performance and recommending to the Contracting Officer changes in requirements; (2) interpreting the statement of work and any other technical performance requirements; (3) performing technical evaluation as required; (4) performing technical inspections and acceptances required by this contract; and (5) assisting in the resolution of technical problems encountered during performance.

The Contracting Officer is the only person with authority to act as agent of the Government under this contract. Only

the Contracting Officer has authority to: (1) direct or negotiate any changes in the statement of work; (2) modify or extend the period of performance; (3) change the delivery schedule; (4) authorize reimbursement to the Contractor for any costs incurred during the performance of this contract; or (5) otherwise change any terms and conditions of this contract.

The Government may unilaterally change its Project Officer designation.

ARTICLE G.2. KEY PERSONNEL, HHSAR 352.270-5 (January 2006)

The key personnel specified in this contract are considered to be essential to work performance. At least 30 days prior to diverting any of the specified individuals to other programs or contracts (or as soon as possible, if an individual must be replaced, for example, as a result of leaving the employ of the Contractor), the Contractor shall notify the Contracting Officer and shall submit comprehensive justification for the diversion or replacement request (including proposed substitutions for key personnel) to permit evaluation by the Government of the impact on performance under this contract. The Contractor shall not divert or otherwise replace any key personnel without the written consent of the Contracting Officer. The Government may modify the contract to add or delete key personnel at the request of the contractor or Government.

The following individual(s) is/are considered to be essential to the work being performed hereunder:

Name	Title

[To be specified in Contract]

ARTICLE G.3. INVOICE SUBMISSION/CONTRACT FINANCING REQUEST AND CONTRACT FINANCIAL REPORT

a. Invoice/Financing Request Instructions and Contract Financial Reporting for NIH Cost-Reimbursement Type Contracts NIH(RC)-4 are attached and made part of this contract. The Contractor shall follow the attached instructions and submission procedures specified below to meet the requirements of a "proper invoice" pursuant to FAR Subpart 32.9, Prompt Payment.

(1) Payment requests shall be submitted as follows:

One original to the following designated billing office:

National Institutes of Health
Office of Financial Management
Commercial Accounts
2115 East Jefferson Street, Room 4B-432, MSC 8500
Bethesda, MD 20892-8500

(2) In addition to the requirements specified in FAR Subpart 32.9 for a proper invoice, the Contractor shall include the following information on all payment requests:

(a) Name of the Office of Acquisitions. The Office of Acquisitions for this contract is National Institute of Allergy and Infectious Diseases.

(b) Central Point of Distribution. For the purpose of this contract, the Central Point of Distribution is NIAID OA Invoices.

(c) Vendor Identification Number. This is the 7 digit number that appears after the Contractor's name in Block 7 of Standard Form 26. ***(Note: This only applies to new contracts awarded on/after June 4, 2007, and any existing contract modified to include the number.)***

(d) DUNS number or DUNS+4 that identifies the Contractor's name and address exactly as stated on the face page of the contract.

(e) Identification of whether payment is to be made using a two-way or three-way match. This contract requires a two-way match.

(b) Inquiries regarding payment of invoices should be directed to the designated billing office, (301) 496-6088.

ARTICLE G.4. INDIRECT COST RATES

In accordance with Federal Acquisition Regulation (FAR) (48 CFR Chapter 1) Clause 52.216-7 (d)(2), Allowable Cost and Payment incorporated by reference in this contract in PART II, SECTION I, the cognizant Contracting Officer representative responsible for negotiating provisional and/or final indirect cost rates is identified as follows:

Director, Division of Financial Advisory Services
Office of Acquisition Management and Policy
National Institutes of Health
6100 Building, Room 6B05
6100 EXECUTIVE BLVD MSC 7540
BETHESDA MD 20892-7540

These rates are hereby incorporated without further action of the Contracting Officer.

ARTICLE G.5. GOVERNMENT PROPERTY

If this RFP will result in the acquisition or use of Government Property provided by the contracting agency or if the Contracting Officer authorizes in the preaward negotiation process, the acquisition of property (other than real property), this ARTICLE will include applicable provisions and incorporate the HHS Publication entitled, **Contractor's Guide for Control of Government Property**, which can be found at:

http://knownet.hhs.gov/log/AgencyPolicy/HHSLogPolicy/contractorsguide.htm

ARTICLE G.6. POST AWARD EVALUATION OF CONTRACTOR PERFORMANCE

a. Contractor Performance Evaluations

Interim and final evaluations of contractor performance will be prepared on this contract in accordance with FAR 42.15. The final performance evaluation will be prepared at the time of completion of work. In addition to the final evaluation, interim evaluation(s) shall be submitted.

Interim and final evaluations will be provided to the Contractor as soon as practicable after completion of the evaluation. The Contractor will be permitted thirty days to review the document and to submit additional information or a rebutting statement. If agreement cannot be reached between the parties, the matter will be referred to an individual one level above the Contracting Officer, whose decision will be final.

Copies of the evaluations, contractor responses, and review comments, if any, will be retained as part of the contract file, and may be used to support future award decisions.

b. Electronic Access to Contractor Performance Evaluations

Contractors that have Internet capability may access evaluations through a secure Web site for review and comment by completing the registration form that can be obtained at the following address:

http://oamp.od.nih.gov/OD/CPS/cps.asp

The registration process requires the contractor to identify an individual that will serve as a primary contact and who will be authorized access to the evaluation for review and comment. In addition, the contractor will be required to identify an alternate contact who will be responsible for notifying the cognizant contracting official in the event the primary contact is unavailable to process the evaluation within the required 30-day time frame.

SECTION H - SPECIAL CONTRACT REQUIREMENTS

ARTICLE H.1. HUMAN SUBJECTS

It is hereby understood and agreed that research involving human subjects shall not be conducted under this contract, and that no material developed, modified, or delivered by or to the Government under this contract, or any subsequent modification of such material, will be used by the Contractor or made available by the Contractor for use by anyone other than the Government, for experimental or therapeutic use involving humans without the prior written approval of the Contracting Officer.

ARTICLE H.2. CONTINUED BAN ON FUNDING OF HUMAN EMBRYO RESEARCH

a. Pursuant to Public Law(s) cited in paragraph b. , below, NIH is prohibited from using appropriated funds to support human embryo research. Contract funds may not be used for (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). The term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.

Additionally, in accordance with a March 4, 1997 Presidential Memorandum, Federal funds may not be used for cloning of human beings.

b. **Public Law and Section No.** **Fiscal Year** **Period Covered**

[Applicable information to be included at award]

ARTICLE H.3. NEEDLE EXCHANGE

a. Pursuant to Public Law(s) cited in paragraph b., below, contract funds shall not be used to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug.

b. **Public Law and Section No.** **Fiscal Year** **Period Covered**

[Applicable information to be included at award]

ARTICLE H.4. PRESS RELEASES

a. Pursuant to Public Law(s) cited in paragraph b., below, the contractor shall clearly state, when issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money: (1) the percentage of the total costs of the program or project which will be financed with Federal money; (2) the dollar amount of Federal funds for the project or program; and (3) the percentage and dollar amount of the total costs of the project or program that will be financed by nongovernmental sources.

b. **Public Law and Section No.** **Fiscal Year** **Period Covered**

[Applicable information to be included at award]

ARTICLE H.5. ANTI -LOBBYING

a. Pursuant to Public Law(s) cited in paragraph c., below, contract funds shall only be used for normal and recognized executive-legislative relationships. Contract funds shall not be used, for publicity or propaganda purposes; or for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself.

b. Contract funds shall not be used to pay salary or expenses of the contractor or any agent acting for the contractor, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature.

c. **Public Law and Section No.** **Fiscal Year** **Period Covered**

[Applicable information to be included at award]

ARTICLE H.6. PRIVACY ACT, HHSAR 352.270-12 (January 2006)

This contract requires the Contractor to perform one or more of the following: (a) Design; (b) develop; or (c) operate a Federal agency system of records to accomplish an agency function in accordance with the Privacy Act of 1974 (Act) (5 U.S.C. 552a(m)(1)) and applicable agency regulations. The term ''system of records'' means a group of any records under the control of any agency from which information is retrieved by the name of the individual or by some identifying number, symbol, or other identifying particular assigned to the individual.

Violations of the Act by the Contractor and/or its employees may result in the imposition of criminal penalties (5 U.S.C. 552a(i)). The Contractor shall ensure that each of its employees knows the prescribed rules of conduct and that each employee is aware that he/she is subject to criminal penalties for violation of the Act to the same extent as HHS employees. These provisions also apply to all subcontracts awarded under this contract which require the design, development or operation of the designated system(s) of records (5 U.S.C. 552a(m)(1)).

The contract work statement: (a) Identifies the system(s) of records and the design, development, or operation work to be performed by the Contractor; and (b) specifies the disposition to be made of such records upon completion of contract performance.

(End of clause)

45 CFR Part 5b contains additional information which includes the rules of conduct and other Privacy Act requirements and can be found at: http://www.access.gpo.gov/nara/cfr/waisidx_06/45cfr5b_06.html.

ARTICLE H.7. OPTION PROVISION

Unless the Government exercises its option pursuant to the Option Clause set forth in ARTICLE I.3., the contract will consist only of the Base Period of the Statement of Work as defined in Sections C and F of the contract. Pursuant to clause 52.217-7 set forth in ARTICLE I.3. of this RFP, the Government may, by unilateral contract modification, require the Contractor to perform additional options set forth in the Statement of Work and also defined in Sections C and F of the contract. If the Government exercises this option, notice must be given at least 30 days prior to the expiration date of this contract, as set forth in Article B.2.d. in Section B of this RFP.

ARTICLE H.8. SUBCONTRACTING PROVISIONS

a. Small Business Subcontracting Plan

(1) The Small Business Subcontracting Plan, dated TBD is attached hereto and made a part of this contract.

(2) The failure of any Contractor or subcontractor to comply in good faith with FAR Clause 52.219-8, entitled

"Utilization of Small Business Concerns" incorporated in this contract and the attached Subcontracting Plan, will be a material breach of such contract or subcontract and subject to the remedies reserved to the Government under FAR Clause 52.219-16 entitled, "Liquidated Damages-Subcontracting Plan."

b. Subcontracting Reports

The Contractor shall submit the following Subcontracting reports electronically via the "electronic Subcontracting Reporting System (eSRS) at http://www.esrs.gov.

(1) Individual Subcontract Reports (ISR)

Regardless of the effective date of this contract, the Report shall be submitted on the following dates for the entire life of this contract:

April 30th
October 30th

(2) Summary Subcontract Report (SSR)

Regardless of the effective date of this contract, the Summary Subcontract Report shall be submitted annually on the following date for the entire life of this contract:

October 30th

For both the Individual and Summary Subcontract Reports, the Contract Specialist shall be included as a contact for notification purposes.

ARTICLE H.9. SALARY RATE LIMITATION LEGISLATION PROVISIONS

a. Pursuant to the P.L.(s) cited in paragraph b., below, no NIH Fiscal Year funds may be used to pay the direct salary of an individual through this contract at a rate in excess of the applicable amount shown or the applicable Executive Level for the fiscal year covered. Direct salary is exclusive of fringe benefits, overhead and general and administrative expenses (also referred to as "indirect costs" or "facilities and administrative (F&A) costs"). Direct salary has the same meaning as the term "institutional base salary." An individual's direct salary (or institutional base salary) is the annual compensation that the contractor pays for an individual's appointment whether that individual's time is spent on research, teaching, patient care or other activities. Direct salary (or institutional base salary) excludes any income that an individual may be permitted to earn outside of duties to the contractor. The annual salary rate limitation also applies to individuals proposed under subcontracts. It does not apply to fees paid to consultants. If this is a multiple year contract, it may be subject to unilateral modifications by the Government if an individual's salary rate used to establish contract funding exceeds any salary rate limitation subsequently established in future HHS appropriation acts.

b. **Public Law and Section No.***	**Fiscal Year***	**Dollar Amount of Salary Limitation***

c. Payment of direct salaries is limited to the Executive Level rate which was in effect on the date(s) the expense was incurred.

[*Applicable information to be included at award]

ARTICLE H.10. INFORMATION SECURITY

The Statement of Work (SOW) requires the contractor to (1) develop, (2) have the ability to access, or (3) host and/or maintain a Federal information system(s). Pursuant to Federal and HHS Information Security Program Policies, the contractor and any subcontractor performing under this contract shall comply with the following requirements:

Federal Information Security Management Act of 2002 (FISMA), Title III, E-Government Act of 2002, Pub. L. No. 107-347 (Dec. 17, 2002); http://csrc.nist.gov/policies/FISMA-final.pdf

a. Information Type

[ ] Administrative, Management and Support Information:

[X] Mission Based Information:

b. Security Categories and Levels

Confidentiality	Level:	**[ ]** Low	**[X]** Moderate	**[ ]** High
Integrity	Level:	**[ ]** Low	**[X]** Moderate	**[ ]** High
Availability	Level:	**[ ]** Low	**[X]** Moderate	**[ ]** High
Overall	**Level:**	**[ ] Low**	**[X] Moderate**	**[ ] High**

c. Position Sensitivity Designations

(1) The following position sensitivity designations and associated clearance and investigation requirements apply under this contract.

[ ] **Level 6: Public Trust - High Risk (Requires Suitability Determination with a BI)**. Contractor employees assigned to a Level 6 position are subject to a Background Investigation (BI).

[X] **Level 5: Public Trust - Moderate Risk (Requires Suitability Determination with NACIC, MBI or LBI)**. Contractor employees assigned to a Level 5 position with no previous investigation and approval shall undergo a National Agency Check and Inquiry Investigation plus a Credit Check (NACIC), a Minimum Background Investigation (MBI), or a Limited Background Investigation (LBI).

[ ] **Level 1: Non Sensitive (Requires Suitability Determination with an NACI)**. Contractor employees assigned to a Level 1 position are subject to a National Agency Check and Inquiry Investigation (NACI).

(2) The contractor shall submit a roster, by name, position, e-mail address, phone number and responsibility, of all staff (including subcontractor staff) working under the contract who will develop, have the ability to access, or host and/or maintain a Federal information system(s). The roster shall be submitted to the Project Officer, with a copy to the Contracting Officer, within 14 calendar days of the effective date of the contract. Any revisions to the roster as a result of staffing changes shall be submitted within 15 calendar days of the change. The Contracting Officer shall notify the contractor of the appropriate level of suitability investigations to be performed. An electronic template, "Roster of Employees Requiring Suitability Investigations," is available for contractor use at: http://ais.nci.nih.gov/forms/Suitability-roster.xls.

Upon receipt of the Government's notification of applicable Suitability Investigations required, the contractor shall complete and submit the required forms within 30 days of the notification. Additional submission instructions can be found at the "NCI Information Technology Security Policies, Background Investigation Process" website: http://ais.nci.nih.gov.

Contractor/subcontractor employees who have met investigative requirements within the past five years may only require an updated or upgraded investigation.

(3) Contractor/subcontractor employees shall comply with the HHS criteria for the assigned position sensitivity designations prior to performing any work under this contract. The following exceptions apply:

Levels 5 and 1: Contractor/subcontractor employees may begin work under the contract after he contractor has submitted the name, position and responsibility of the employee to the Project Officer, as described in paragraph c. (2) above.

Level 6: In special circumstances the Project Officer may request a waiver of the pre-appointment investigation. If the waiver is granted, the Project Officer will provide written authorization for the contractor/subcontractor employee to work under the contract.

d. Information Security Training

The contractor shall ensure that each contractor/subcontractor employee has completed the NIH Computer Security Awareness Training course at: http://irtsectraining.nih.gov/ prior to performing any contract work, and thereafter completing the NIH-specified fiscal year refresher course during the period of performance of the contract.

The contractor shall maintain a listing by name and title of each contractor/subcontractor employee working under this contract that has completed the NIH required training. Any additional security training completed by contractor/subcontractor staff shall be included on this listing. The listing of completed training shall be included in the first technical progress report. (See Article C.2. Reporting Requirements.) Any revisions to this listing as a result of staffing changes shall be submitted with next required technical progress report.

e. Rules of Behavior

The contractor/subcontractor employees shall comply with the NIH Information Technology General Rules of Behavior at: http://irm.cit.nih.gov/security/nihitrob.html.

f. Personnel Security Responsibilities

Contractor Notification of New and Departing Employees Requiring Background Investigations

(1) The contractor shall notify the Contracting Officer, the Project Officer, and the Security Investigation Reviewer within **five working days** before a new employee assumes a position that requires a suitability determination or when an employee with a security clearance stops working under the contract. The government will initiate a background investigation on new employees requiring security clearances and will stop pending background investigations for employees that no longer work under the contract.

(2) New employees: Provide the name, position title, e-mail address, and phone number of the new employee. Provide the name, position title and suitability level held by the former incumbent. If the employee is filling a new position, provide a description of the position and the government will determine the appropriate security level.

(3) Departing employees:

- Provide the name, position title, and security clearance level held by or pending for the individual.
- Perform and document the actions identified in the "Employee Separation Checklist", attached in Section J, ATTACHMENTS of this contract, when a contractor/subcontractor employee terminates work under this contract. All documentation shall be made available to the Project Officer and/or Contracting Officer upon request.

g. Commitment to Protect Non-Public Departmental Information Systems and Data

(1) Contractor Agreement

The Contractor and its subcontractors performing under this SOW shall not release, publish, or disclose non-public Departmental information to unauthorized personnel, and shall protect such information in accordance with provisions of the following laws and any other pertinent laws and regulations governing the confidentiality of such information:

-18 U.S.C. 641 (Criminal Code: Public Money, Property or Records)
-18 U.S.C. 1905 (Criminal Code: Disclosure of Confidential Information)
-Public Law 96-511 (Paperwork Reduction Act)

(2) Contractor-Employee Non-Disclosure Agreements

Each contractor/subcontractor employee who may have access to non-public Department information under this contract shall complete the Commitment to Protect Non-Public Information - Contractor Agreement. A copy of each signed and witnessed Non-Disclosure agreement shall be submitted to the Project Officer prior to performing any work under the contract.

h. NIST SP 800-26 Self-Assessment Questionnaire

The contractor shall annually update and re-submit its Self-Assessment Questionnaire required by NIST Draft SP 800-26, Revision 1, Guide for Information Security Program Assessments and System Reporting Form (http://csrc.nist.gov/publications/drafts/Draft-sp800-26Rev1.pdf - See Appendix B for format).

Subcontracts: The contractor's annual update to its Self-Assessment Questionnaire shall include similar information for any subcontractor that performs under the SOW to (1) develop a Federal information system(s) at the contractor's/subcontractor's facility, or (2) host and/or maintain a Federal information system(s) at the contractor's/subcontractor's facility.

The annual update shall be submitted to the Project Officer, with a copy to the Contracting Office no later than the completion date of the period of performance.

i. Information System Security Plan

The contractor's draft ISSP submitted with its proposal shall be finalized in coordination with the Project Officer no later than 90 calendar days after contract award.

Following approval of its draft ISSP, the contractor shall update and resubmit its ISSP to the Project Officer every three years or when a major modification has been made to its internal system. The contractor shall use the current ISSP template in Appendix A of NIST SP 800-18, *Guide to Developing Security Plans for Federal Information Systems*. (http://csrc.nist.gov/publications/nistpubs/800-18-Rev1/sp800-18-Rev1-final.pdf). The details contained in the contractor's ISSP shall be commensurate with the size and complexity of the requirements of the SOW based on the System Categorization determined above in subparagraph (b) Security Categories and Levels of this Article.

Subcontracts: The contractor shall include similar information for any subcontractor performing under the SOW with the contractor whenever the submission of an ISSP is required.

ARTICLE H.11. STORAGE FACILITY REQUIREMENTS AND CERTIFICATION

The contractor shall ensure that all materials generated under this contract for which commercial records storage is required, shall be stored in a facility that meets National Archives and Records Administration (NARA) requirements for safe, secure and certified storage as required by 36 CFR 1228, subpart K.

The contractor shall provide the contracting officer with the name(s) and location(s) of the commercial records storage facility used to store materials under this contract. In addition, the contractor shall provide a copy of the "Facility Standards for Records Storage Facilities Inspection Checklist," self-certifying that the facility being used to store federal records meets established NARA standards. NARA Standards are available at:
http://www.archives.gov/about/regulations/part-1228/k.html

Sixty (60) days prior to contract end date, the contractor shall submit to the Project Officer and Contracting Officer, an inventory of all materials stored. The disposition of these materials shall be determined no later than the expiration date of the contract.

ARTICLE H.12. ELECTRONIC AND INFORMATION TECHNOLOGY ACCESSIBILITY HHSAR 352.270-19 (January 2006)

Pursuant to Section 508 of the Rehabilitation Act of 1973 (29 U.S.C. 794d) as amended by Public Law 105–220 under Title IV (Rehabilitation Act Amendments of 1998), all Electronic and Information Technology (EIT) developed, procured, maintained, and/or used under this contract shall be in compliance with the ''Electronic and Information Technology Accessibility Standards'' set forth by the Architectural and Transportation Barriers Compliance Board (also referred to as the ''Access Board'') in 36 CFR part 1194. The complete text of Section 508 Final Standards can be accessed at http://www.access-board.gov/sec508/standards.htm.

The standards applicable to this requirement are listed below:

Vendors may document conformance using industry-standard Voluntary Product Accessibility Template at http://www.itic.org/archives/articles/20040506/faq_voluntary_product_accessibility_template_vpat.php. Vendors should provide detailed information necessary for determining compliance, including defined contractor-incidental exceptions.

(End of clause)

ARTICLE H.13. ENERGY STAR REQUIREMENTS

Executive Order 13123, "Greening the Government Through Efficient Energy Management" and FAR 23.203 require that when Federal Agencies acquire energy using products, they select, where life-cycle cost-effective, and available, ENERGY STAR® or other energy efficient products.

Unless the Contracting Officer determines otherwise, all energy-using products acquired under this contract must be either an ENERGY STAR® or other energy efficient product designated by the Department of Energy's Federal Energy Management Program (FEMP).

For more information about ENERGY STAR® see http://www.energystar.gov/
For more information about FEMP see http://www.eere.energy.gov/

ARTICLE H.14. PUBLICATION AND PUBLICITY

In addition to the requirements set forth in HHSAR Clause **352.270-6, Publications and Publicity** incorporated by reference in SECTION I of this contract, the contractor shall acknowledge the support of the National Institutes of Health whenever publicizing the work under this contract in any media by including an acknowledgment substantially as follows:

"This project has been funded in whole or in part with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. TBD.

ARTICLE H.15. REPORTING MATTERS INVOLVING FRAUD, WASTE AND ABUSE

Anyone who becomes aware of the existence or apparent existence of fraud, waste and abuse in NIH funded programs is encouraged to report such matters to the HHS Inspector General's Office in writing or on the Inspector General's Hotline. The toll free number is **1-800-HHS-TIPS** (**1-800-447-8477).** All telephone calls will be handled confidentially. The e-mail address is **Htips@os.dhhs.gov** and the mailing address is:

Office of Inspector General
Department of Health and Human Services
TIPS HOTLINE
P.O. Box 23489
Washington, D.C. 20026

ARTICLE H.16. YEAR 2000 COMPLIANCE

In accordance with FAR 39.106, Information Technology acquired under this contract must be Year 2000 compliant as set forth in the following clause(s):

1. Service Involving the Use of Information Technology

YEAR 2000 COMPLIANCE--SERVICE INVOLVING THE USE OF INFORMATION TECHNOLOGY

The Contractor agrees that each item of hardware, software, and firmware used under this contract shall be able to accurately process date data (including, but not limited to, calculating, comparing and sequencing) from, into and between the twentieth and twenty-first centuries and the Year 1999 and the Year 2000 and leap year calculations.

(End of Clause)

2. Noncommercial Supply Items Warranty

YEAR 2000 WARRANTY--NONCOMMERCIAL SUPPLY ITEMS

The contractor warrants that each noncommercial item of hardware, software, and firmware delivered or developed under this contract and listed below shall be able to accurately process date data (including, but not limited to, calculating, comparing and sequencing) from, into and between the twentieth and twenty-first centuries and the Year 1999 and the Year 2000 and leap year calculations, when used in accordance with the item documentation provided by the contractor, provided that all listed or unlisted items (e.g., hardware, software and firmware) used in combination with such listed item properly exchange date data with it. If the contract requires that specific listed items must perform as a system in accordance with the foregoing warranty, then that warranty shall apply to those listed items as a system. The duration of this warranty and the remedies available to the Government for breach of this warranty shall be as defined in, and subject to, the terms and limitations of any general warranty provisions of this contract provided that notwithstanding any provision to the contrary in such warranty provision(s), or in the absence of any such warranty provision(s), the remedies available to the Government under this warranty shall include repair or replacement of any listed item whose noncompliance is discovered and made known to the contractor in writing within ninety (90) days after acceptance. Nothing in this warranty shall be construed to limit any rights or remedies the Government may otherwise have under this contract with respect to defects other than Year 2000 performance.

YEAR 2000 COMPLIANT ITEMS

_____

_____

_____

(End of Clause)

3. Commercial Supply Products Warranty

YEAR 2000 WARRANTY--COMMERCIAL SUPPLY ITEMS

The contractor warrants that each hardware, software and firmware product delivered under this contract and listed below shall be able to accurately process date data (including, but not limited to, calculating, comparing, and sequencing) from, into, and between the twentieth and twenty-first centuries and the Year 1999 and the Year 2000 and leap year calculations, when used in accordance with the product documentation provided by the contractor, provided that all listed or unlisted products (e.g., hardware, software, firmware) used in combination with such listed product properly exchange date data with it. If the contract requires that specific listed products must perform as a system in accordance with the foregoing warranty, then that warranty shall apply to those listed products as a system. The duration of this warranty and the remedies available to the Government for breach of this warranty shall be as defined in, and subject to, the terms and limitations of the contractor's standard commercial warranty or warranties contained in this contract, provided that notwithstanding any provision to the contrary in such commercial warranty or warranties, the remedies available to the Government under this warranty shall include repair or replacement of any listed product whose non-compliance is discovered and made known to the contractor in writing within ninety (90) days after acceptance. Nothing in this warranty shall be construed to limit any rights or remedies the Government may otherwise have under this contract with

respect to defects other than Year 2000 performance.

YEAR 2000 COMPLIANT ITEMS

(End of Clause)

ARTICLE H.17. SHARING RESEARCH DATA

The data sharing plan submitted by the contractor is acceptable and is hereby incorporated by reference. The contractor agrees to adhere to its plan and shall request prior approval of the Contracting Officer for any changes in its plan.

The NIH endorses the sharing of final research data to expedite the translation of research results into knowledge, products, and procedures to improve human health. This contract is expected to generate research data that must be shared with the public and other researchers. NIH's data sharing policy may be found at the following Web site:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html

NIH recognizes that data sharing may be complicated or limited, in some cases, by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule (see HHS-published documentation on the Privacy Rule at http://www.hhs.gov/ocr/). The rights and privacy of people who participate in NIH-funded research must be protected at all times; thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects.

ARTICLE H.18. HOTEL AND MOTEL FIRE SAFETY ACT OF 1990 (P.L. 101-391)

Pursuant to Public Law 101-391, no Federal funds may be used to sponsor or fund in whole or in part a meeting, convention, conference or training seminar that is conducted in, or that otherwise uses the rooms, facilities, or services of a place of public accommodation that do not meet the requirements of the fire prevention and control guidelines as described in the Public Law. This restriction applies to public accommodations both foreign and domestic.

Public accommodations that meet the requirements can be accessed at: http://www.usfa.fema.gov/hotel/index.htm

ARTICLE H.19. PROHIBITION ON CONTRACTOR INVOLVEMENT WITH TERRORIST ACTIVITIES

The contractor acknowledges that U.S. Executive Orders and Laws, including but not limited to E.O. 13224 and P.L. 107-56, prohibit transactions with, and the provision of resources and support to, individuals and organizations associated with terrorism. It is the legal responsibility of the contractor to ensure compliance with these Executive Orders and Laws. This clause must be included in all subcontracts issued under this contract.

ARTICLE H.20. NIH POLICY ON ENHANCING PUBLIC ACCESS TO ARCHIVED PUBLICATIONS RESULTING FROM NIH-FUNDED RESEARCH

The Policy requests that beginning May 2, 2005, NIH-funded investigators submit to the NIH National Library of Medicine's (NLM) PubMed Central (PMC) an electronic version of the author's final manuscript, upon acceptance for publication, resulting from research supported in whole or in part with direct costs from NIH. NIH defines the author's final manuscript as the final version accepted for journal publication, and includes all modifications from the publishing peer review process. The PMC archive will preserve permanently these manuscripts for use by the public, health care providers, educators, scientists, and NIH. The Policy directs electronic submissions to the NIH/NLM/PMC: http://www.pubmedcentral.nih.gov.

Additional information is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-022.html.

ARTICLE H.21. CONSTITUTION DAY

Each educational institution that receives Federal funds for a fiscal year shall hold an educational program on the United States Constitution on September 17 of such year for the students serviced by the educational institution in accordance with Public Law 108-447.

PART II - CONTRACT CLAUSES

SECTION I - CONTRACT CLAUSES

THE FOLLOWING **ARTICLE I.1 GENERAL CLAUSE LISTING(S)** WILL BE APPLICABLE TO MOST CONTRACTS RESULTING FROM THIS RFP. HOWEVER, THE ORGANIZATIONAL STRUCTURE OF THE SUCCESSFUL OFFEROR(S) WILL DETERMINE THE SPECIFIC GENERAL CLAUSE LISTING TO BE CONTAINED IN THE CONTRACT(S) AWARDED FROM THIS RFP:

General Clauses for a Cost-Reimbursement Research and Development Contract
General Clauses for a Cost-Reimbursement Contract with Educational Institutions
General Clauses for a Cost-Reimbursement Contract with Non-Profit Organizations Other Than Educational Institutions

The complete listing of these clauses may be accessed at:
http://rcb.cancer.gov/rcb-internet/appl/general-clauses/clauses.jsp

ARTICLE I.1. GENERAL CLAUSES FOR A COST-REIMBURSEMENT RESEARCH AND DEVELOPMENT CONTRACT - FAR 52.252-2, CLAUSES INCORPORATED BY REFERENCE (FEBRUARY 1998)

This contract incorporates the following clauses by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available. Also, the full text of a clause may be accessed electronically at this address: http://www.acquisition.gov/comp/far/index.html.

a. FEDERAL ACQUISITION REGULATION (FAR) (48 CFR CHAPTER 1) CLAUSES:

FAR CLAUSE NO.	DATE	TITLE
52.202-1	Jul 2004	Definitions (Over $100,000)
52.203-3	Apr 1984	Gratuities (Over $100,000)
52.203-5	Apr 1984	Covenant Against Contingent Fees (Over $100,000)
52.203-6	Sep 2006	Restrictions on Subcontractor Sales to the Government (Over $100,000)
52.203-7	Jul 1995	Anti-Kickback Procedures (Over $100,000)
52.203-8	Jan 1997	Cancellation, Rescission, and Recovery of Funds for Illegal or Improper Activity (Over $100,000)
52.203-10	Jan 1997	Price or Fee Adjustment for Illegal or Improper Activity (Over $100,000)
52.203-12	Sep 2005	Limitation on Payments to Influence Certain Federal Transactions (Over $100,000)
52.204-4	Aug 2000	Printed or Copied Double-Sided on Recycled Paper (Over $100,000)
52.204-7	Jul 2006	Central Contractor Registration
52.209-6	Sep 2006	Protecting the Government's Interests When Subcontracting With Contractors Debarred, Suspended, or Proposed for Debarment (Over $30,000)
52.215-2	Jun 1999	Audit and Records - Negotiation (Over $100,000)
52.215-8	Oct 1997	Order of Precedence - Uniform Contract Format
52.215-10	Oct 1997	Price Reduction for Defective Cost or Pricing Data (Over $650,000)
52.215-12	Oct 1997	Subcontractor Cost or Pricing Data (Over $650,000)
52.215-14	Oct 1997	Integrity of Unit Prices (Over $100,000)
52.215-15	Oct 2004	Pension Adjustments and Asset Reversions
52.215-18	Jul 2005	Reversion or Adjustment of Plans for Post-Retirement Benefits (PRB) other than Pensions
52.215-19	Oct 1997	Notification of Ownership Changes
52.215-21	Oct 1997	Requirements for Cost or Pricing Data or Information Other Than Cost or Pricing Data - Modifications
52.216-7	Dec 2002	Allowable Cost and Payment
52.216-8	Mar 1997	Fixed Fee
52.219-8	May 2004	Utilization of Small Business Concerns (Over $100,000)

52.219-9	Sep 2006	Small Business Subcontracting Plan (Over $550,000, $1,000,000 for Construction)
52.219-16	Jan 1999	Liquidated Damages - Subcontracting Plan (Over $550,000, $1,000,000 for Construction)
52.222-2	Jul 1990	Payment for Overtime Premium (Over $100,000) (Note: The dollar amount in paragraph (a) of this clause is $0 unless otherwise specified in the contract.)
52.222-3	Jun 2003	Convict Labor
52.222-21	Feb 1999	Prohibition of Segregated Facilities
52.222-26	Mar 2007	Equal Opportunity
52.222-35	Sep 2006	Equal Opportunity for Special Disabled Veterans, Veterans of the Vietnam Era, and Other Eligible Veterans (Over $100,000)
52.222-36	Jun 1998	Affirmative Action for Workers with Disabilities
52.222-37	Sep 2006	Employment Reports on Special Disabled Veterans, Veterans of the Vietnam Era, and Other Eligible Veterans (Over $100,000)
52.222-50	Apr 2006	Combating Trafficking in Persons
52.223-6	May 2001	Drug-Free Workplace
52.223-14	Aug 2003	Toxic Chemical Release Reporting (Over $100,000)
52.225-1	Jun 2003	Buy American Act - Supplies
52.225-13	Feb 2006	Restrictions on Certain Foreign Purchases
52.227-1	Jul 1995	Authorization and Consent, Alternate I (Apr 1984)
52.227-2	Aug 1996	Notice and Assistance Regarding Patent and Copyright Infringement (Over $100,000)
52.227-11	Jun 1997	Patent Rights - Retention by the Contractor (Short Form) (Note: In accordance with FAR 27.303(a)(2), paragraph (f) is modified to include the requirements in FAR 27.303(a)(2)(i) through (iv). The frequency of reporting in (i) is annual.
52.227-14	Jun 1987	Rights in Data - General
52.232-9	Apr 1984	Limitation on Withholding of Payments
52.232-17	Jun 1996	Interest (Over $100,000)
52.232-20	Apr 1984	Limitation of Cost
52.232-23	Jan 1986	Assignment of Claims
52.232-25	Oct 2003	Prompt Payment, Alternate I (Feb 2002)
52.232-33	Oct 2003	Payment by Electronic Funds Transfer--Central Contractor Registration
52.233-1	Jul 2002	Disputes
52.233-3	Aug 1996	Protest After Award, Alternate I (Jun 1985)
52.233-4	Oct 2004	Applicable Law for Breach of Contract Claim

52.242-1	Apr 1984	Notice of Intent to Disallow Costs
52.242-3	May 2001	Penalties for Unallowable Costs (Over $650,000)
52.242-4	Jan 1997	Certification of Final Indirect Costs
52.242-13	Jul 1995	Bankruptcy (Over $100,000)
52.243-2	Aug 1987	Changes - Cost Reimbursement, Alternate V (Apr 1984)
52.244-2	Aug 1998	Subcontracts, Alternate I (January 2006)
52.244-5	Dec 1996	Competition in Subcontracting (Over $100,000)
52.244-6	Mar 2007	Subcontracts for Commercial Items
52.245-5	May 2004	Government Property (Cost-Reimbursement, Time and Material, or Labor-Hour Contract)
52.245-9	Aug 2005	Use and Charges
52.246-23	Feb 1997	Limitation of Liability (Over $100,000)
52.249-6	Sep 1996	Termination (Cost-Reimbursement)
52.249-14	Apr 1984	Excusable Delays
52.253-1	Jan 1991	Computer Generated Forms

b. DEPARTMENT OF HEALTH AND HUMAN SERVICES ACQUISITION REGULATION (HHSAR) (48 CFR CHAPTER 3) CLAUSES:

HHSAR CLAUSE NO.	DATE	TITLE
352.202-1	Jan 2001	Definitions - with Alternate paragraph (h) (Jan 2006)
352.216-72	Jan 2006	Additional Cost Principles
352.228-7	Dec 1991	Insurance - Liability to Third Persons
352.232-9	Jan 2006	Withholding of Contract Payments
352.233-70	Jan 2006	Litigation and Claims
352.242-71	Apr 1984	Final Decisions on Audit Findings
352.270-5	Jan 2006	Key Personnel
352.270-6	Jan 2006	Publications and Publicity
352.270-10	Jan 2006	Anti-Lobbying

[End of GENERAL CLAUSES FOR A COST-REIMBURSEMENT RESEARCH AND DEVELOPMENT CONTRACT - Rev. 03/2007].

ARTICLE I.2. AUTHORIZED SUBSTITUTIONS OF CLAUSES

Any authorized substitutions and/or modifications other than the General Clauses which will be based on the type of contract/Contractor will be determined during negotiations.

It is expected that the following substitution(s) will be made part of the resultant contract:

FAR Clauses **52.215-15, Pension Adjustments And Asset Reversions** (October 2004); **52.215-18, Reversion Or Adjustment Of Plans For Post Retirement Benefits (PRB) Other Than Pensions** (July 2005); and, **52.215-19, Notification Of Ownership Changes** (October 1997), are deleted in their entirety.

Alternate IV (October 1997) of FAR Clause **52.215-21, Requirements For Cost Or Pricing Data Or Information Other Than Cost Or Pricing Data--Modifications** (October 1997) is added.

Alternate II (October 2001) of FAR Clause **52.219-9, Small Business Subcontracting Plan** (September 2006) is added.

FAR Clause **52.232-20, Limitation Of Cost** (April 1984), is deleted in its entirety and FAR Clause **52.232-22, Limitation Of Funds** (April 1984) is substituted therefor. ***[NOTE: When this contract is fully funded, FAR Clause 52.232-22, LIMITATION OF FUNDS will no longer apply and FAR Clause 52.232-20, LIMITATION OF COST will become applicable.]***

ARTICLE I.3. ADDITIONAL CONTRACT CLAUSES

Additional clauses other than those listed below which are based on the type of contract/Contractor shall be determined during negotiations. Any contract awarded from this solicitation will contain the following:

This contract incorporates the following clauses by reference, (unless otherwise noted), with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available.

a. FEDERAL ACQUISITION REGULATION (FAR) (48 CFR CHAPTER 1) CLAUSES

(1) FAR Clause **52.215-17, Waiver of Facilities Capital Cost of Money** (October 1997).

(2) FAR Clause **52.217-7, Option for Increased Quantity - Separately Priced Line Item** (March 1989).

"....The Contracting Officer may exercise the option by written notice to the Contractor within 30 days.

(3) FAR Clause **52.217-9, Option to Extend the Term of the Contract** (March 2000).

"(a) The Government may extend the term of this contract by written notice to the Contractor within 7 days; provided that the Government gives the Contractor a preliminary written notice of its intent to extend at least 30 days before the contract expires. The preliminary notice does not commit the Government to an extension.

(c) The total duration of this contract, including the exercise of any options under this clause, shall not exceed 84 months, unless otherwise agreed by the parties and authorized by the Contracting Officer.

(4) FAR Clause **52.219-4, Notice of Price Evaluation Preference for HUBZone Small Business Concerns** (July 2005).

"(c) Waiver of evaluation preference.....

[ ] Offeror elects to waive the evaluation preference."

(5) FAR Clause **52.222-29, Notification of Visa Denial** (June 2003).

(6) FAR Clause **52.224-1, Privacy Act Notification** (April 1984).

(7) FAR Clause **52.224-2, Privacy Act** (April 1984).

(8) FAR Clause **52.227-14, Rights in Data - General** (June 1987).

(9) **Alternate II** (June 1987), FAR Clause **52.227-14, Rights in Data--General** (June 1987).

Additional purposes for which the limited rights data may be used are:

(10) **Alternate III** (June 1987), FAR Clause **52.227-14, Rights in Data--General** (June 1987).

Additions to, or limitations on, the restricted rights set forth in the Restricted Rights Notice of subparagraph (g)(3) of the clause are expressly stated as follows:

(11) **Alternate V** (June 1987), FAR Clause **52.227-14, Rights in Data--General** (June 1987).

Specific data items that are not subject to paragraph (j) include:

(12) FAR Clause **52.227-16, Additional Data Requirements** (June 1987).

(13) FAR Clause **52.227-17, Rights in Data--Special Works** (June 1987).

(14) FAR Clause **52.229-8, Taxes-Foreign Cost-Reimbursement Contracts** (March 1990).

(15) FAR Clause **52.239-1, Privacy or Security Safeguards** (August 1996).

(16) FAR Clause **52.242-3, Penalties for Unallowable Costs** (May 2001).

(17) FAR Clause **52.247-63, Preference for U.S. Flag Air Carriers** (June2003).

b. DEPARTMENT OF HEALTH AND HUMAN SERVICES ACQUISITION REGULATION (HHSAR) (48 CHAPTER 3) CLAUSES:

(1) HHSAR Clause **352.224-70, Confidentiality of Information** (January 2006).

(2) HHSAR Clause **352.270-1, Accessibility of Meetings, Conferences and Seminars to Persons with Disabilities** (January 2001).

c. NATIONAL INSTITUTES OF HEALTH (NIH) RESEARCH CONTRACTING (RC) CLAUSES:

The following clauses are attached and made a part of this contract:

(1) **NIH (RC)-7, Procurement of Certain Equipment** (April 1984) (OMB Bulletin 81-16).

ARTICLE I.4. ADDITIONAL FAR CONTRACT CLAUSES INCLUDED IN FULL TEXT

Additional clauses other than those listed below which are based on the type of contract/Contractor shall be determined during negotiations. Any contract awarded from this solicitation will contain the following:

This contract incorporates the following clauses in full text.

FEDERAL ACQUISITION REGULATION (FAR)(48 CFR CHAPTER 1) CLAUSES:

a. FAR Clause **52.222-39, Notification Of Employee Rights Concerning Payment Of Union Dues Or Fees** (December 2004)

(a) Definition. As used in this clause--

United States means the 50 States, the District of Columbia, Puerto Rico, the Northern Mariana Islands, American Samoa, Guam, the U.S. Virgin Islands, and Wake Island.

(b) Except as provided in paragraph (e) of this clause, during the term of this contract, the Contractor shall post a notice, in the form of a poster, informing employees of their rights concerning union membership and payment of union dues and fees, in conspicuous places in and about all its plants and offices, including all places where notices to employees are customarily posted. The notice shall include the following information (except that the information pertaining to National Labor Relations Board shall not be included in notices posted in the plants or offices of carriers subject to the Railway Labor Act, as amended (45 U.S.C. 151-188)).

Notice to Employees

Under Federal law, employees cannot be required to join a union or maintain membership in a union in order to retain their jobs. Under certain conditions, the law permits a union and an employer to enter into a union-security agreement requiring employees to pay uniform periodic dues and initiation fees. However, employees who are not union members can object to the use of their payments for certain purposes and can only be required to pay their share of union costs relating to collective bargaining, contract administration, and grievance adjustment.

If you do not want to pay that portion of dues or fees used to support activities not related to collective bargaining, contract administration, or grievance adjustment, you are entitled to an appropriate reduction in your payment. If you believe that you have been required to pay dues or fees used in part to support activities not related to collective bargaining, contract administration, or grievance adjustment, you may be entitled to a refund and to an appropriate reduction in future payments.

For further information concerning your rights, you may wish to contact the National Labor Relations Board (NLRB) either at one of its Regional offices or at the following address or toll free number:

National Labor Relations Board
Division of Information
1099 14th Street, N.W.
Washington, DC 20570
1-866-667-6572
1-866-316-6572 (TTY)

To locate the nearest NLRB office, see NLRB's website at http://www.nlrb.gov.

(c) The Contractor shall comply with all provisions of Executive Order 13201 of February 17, 2001, and related implementing regulations at 29 CFR part 470, and orders of the Secretary of Labor.

(d) In the event that the Contractor does not comply with any of the requirements set forth in paragraphs (b), (c), or (g), the Secretary may direct that this contract be cancelled, terminated, or suspended in whole or in part, and declare the Contractor ineligible for further Government contracts in accordance with procedures at 29 CFR part 470, Subpart B--Compliance Evaluations, Complaint Investigations and Enforcement Procedures. Such other sanctions or remedies may be imposed as are provided by 29 CFR part 470, which implements Executive Order 13201, or as are otherwise provided by law.

(e) The requirement to post the employee notice in paragraph (b) does not apply to--

(1) Contractors and subcontractors that employ fewer than 15 persons;

(2) Contractor establishments or construction work sites where no union has been formally recognized by the Contractor or certified as the exclusive bargaining representative of the Contractor's employees;

(3) Contractor establishments or construction work sites located in a jurisdiction named in the definition of the United States in which the law of that jurisdiction forbids enforcement of union-security agreements;

(4) Contractor facilities where upon the written request of the Contractor, the Department of Labor Deputy Assistant Secretary for Labor-Management Programs has waived the posting requirements with respect to any of the Contractor's facilities if the Deputy Assistant Secretary finds that the Contractor has demonstrated that--

(i) The facility is in all respects separate and distinct from activities of the Contractor related to the performance of a contract; and
(ii) Such a waiver will not interfere with or impede the effectuation of the Executive order; or

(5) Work outside the United States that does not involve the recruitment or employment of workers within the United States.

(f) The Department of Labor publishes the official employee notice in two variations; one for contractors covered by the Railway Labor Act and a second for all other contractors. The Contractor shall--

(1) Obtain the required employee notice poster from the Division of Interpretations and Standards, Office of Labor-Management Standards, U.S. Department of Labor, 200 Constitution Avenue, NW, Room N-5605, Washington, DC 20210, or from any field office of the Department's Office of Labor-Management Standards or Office of Federal Contract Compliance Programs;

(2) Download a copy of the poster from the Office of Labor-Management Standards website at http://www.olms.dol.gov; or

(3) Reproduce and use exact duplicate copies of the Department of Labor's official poster.

(g) The Contractor shall include the substance of this clause in every subcontract or purchase order that exceeds the simplified acquisition threshold, entered into in connection with this contract, unless exempted by the Department of Labor Deputy Assistant Secretary for Labor-Management Programs on account of special circumstances in the national interest under authority of 29 CFR 470.3(c). For indefinite quantity subcontracts, the Contractor shall include the substance of this clause if the value of orders in any calendar year of the subcontract is expected to exceed the simplified acquisition threshold. Pursuant to 29 CFR part 470, Subpart B--Compliance Evaluations, Complaint Investigations and Enforcement Procedures, the Secretary of Labor may direct the Contractor to take such action in the enforcement of these regulations, including the imposition of sanctions for noncompliance with respect to any such subcontract or purchase order. If the Contractor becomes involved in litigation with a subcontractor or vendor, or is threatened with such involvement, as a result of such direction, the Contractor may request the United States, through the Secretary of Labor, to enter into such litigation to protect the interests of the United States.

PART III - LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACHMENTS

SECTION J - LIST OF ATTACHMENTS

The following documents are incorporated into this RFP:

SOLICITATION ATTACHMENTS:

Attachment No.	Title	Location
Attachment 1:	Packaging and Delivery of Proposal	See Attachment Section at the end of this RFP
Attachment 2:	Statement of Work	See Attachment Section at the end of this RFP.
Attachment 3:	Reporting Requirements and Deliverables	See Attachment Section at the end of this RFP
Attachment 4:	Additional Technical Proposal Instructions and Format For Technical Proposal	See Attachment Section at the end of this RFP.
Attachment 5:	Additional Business Proposal Instructions and Uniform Cost Assumptions	See Attachment Section at the end of this RFP.
Attachment 6:	Additional RFP Materials	See Attachment Section at the end of this RFP.
Attachment 7:	Proposal Intent to Respond Sheet	**http://www.niaid.nih.gov/contract/forms.htm**

TECHNICAL PROPOSAL ATTACHMENTS: (The following attachments must be completed, where applicable, and submitted with the Technical Proposal.)

Attachment No.	Title	Location
Attachment 8:	Technical Proposal Cost Summary	**http://www.niaid.nih.gov/contract/forms.htm**
Attachment 9:	Summary of Related Activities	**http://www.niaid.nih.gov/contract/forms.htm**
Attachment 10:	Government Notice for Handling Proposals	**http://www.niaid.nih.gov/contract/forms/form7.pdf**
Attachment 11:	Project Objectives, NIH 1688-1	**http://rcb.cancer.gov/rcb-internet/forms/nih1688-1.pdf**

BUSINESS PROPOSAL ATTACHMENTS: (The following attachments must be completed, where applicable, and submitted with the Business Proposal.)

Attachment No.	Title	Location
Attachment 12:	Proposal Summary and Data Record, NIH-2043	http://www.niaid.nih.gov/contract/forms.htm
Attachment 13:	Small Business Subcontracting Plan	**http://rcb.cancer.gov/rcb-internet/forms/SBA Plan Nov 2005.pdf**

Attachment 14:	Breakdown of Proposed Estimated Costs (plus Fee) with Excel Spreadsheet	http://oamp.od.nih.gov/contracts/BUSCOST.HTM http://oamp.od.nih.gov/Division/DFAS/spshexcl.xls
Attachment 15:	Offeror's Points of Contact	**http://www.niaid.nih.gov/contract/forms.htm**
Attachment 16:	Disclosure of Lobbying Activities, OMB Form SF-LLL	http://rcb.cancer.gov/rcb-internet/forms/sflllin.pdf

INFORMATIONAL ATTACHMENTS: (The following Attachments and Reports will become part of any contract resulting from this RFP and will be required during contract performance.)

Attachment No.	Title	Location
Attachment 17:	Invoice/Financing Request and Contract Financial Reporting Instructions--Cost Reimbursement, NIH(RC)-4	http://rcb.cancer.gov/rcb-internet/forms/rc4.pdf
Attachment 18:	Privacy Act System of Records *System of Records No. 09-25-0099 is applicable to this RFP.*	http://oma.od.nih.gov/ms/privacy/pa-files/read02systems.htm
Attachment 19:	Procurement of Certain Equipment, NIH(RC)-7	**http://www.niaid.nih.gov/contract/forms/NIH-RC-7.pdf**
Attachment 20:	Government Property Schedule	**http://www.niaid.nih.gov/contract/forms/form9.pdf**
Attachment 21:	Disclosure of Lobbying Activities, OMB Form SF-LLL	http://rcb.cancer.gov/rcb-internet/forms/sflllin.pdf
Attachment 22:	Commitment To Protect Non-Public Information Contractor Agreement	http://irm.cit.nih.gov/security/Nondisclosure.pdf
Attachment 23:	Roster of Employees Requiring Suitability Investigations	http://ais.nci.nih.gov/forms/Suitability-roster.xls
Attachment 24:	Employee Separation Checklist	**http://rcb.cancer.gov/rcb-internet/forms/Emp-sep-checklist.pdf**

PART IV - REPRESENTATIONS AND INSTRUCTIONS

SECTION K - REPRESENTATIONS, CERTIFICATIONS AND OTHER STATEMENTS OF OFFERORS

IF YOU INTEND TO SUBMIT A PROPOSAL, YOU MUST :

1. Go to the Online Representations and Certifications Application (ORCA) at: https://orca.bpn.gov/ and complete the Representations and Certifications; and

2. Complete, and include as part of your BUSINESS PROPOSAL, SECTION K which can be accessed electronically from the INTERNET at the following address:
   http://rcb.cancer.gov/rcb-internet/wkf/sectionk.pdf

If you are unable to access this document electronically, you may request a copy from the Contracting Officer identified on the cover page of this solicitation.

SECTION L - INSTRUCTIONS, CONDITIONS AND NOTICES TO OFFERORS

1. GENERAL INFORMATION

a. **INSTRUCTIONS TO OFFERORS--COMPETITIVE ACQUISITION** [FAR Provision 52.215-1 (January 2004)]

(a) *Definitions*. As used in this provision--

Discussions are negotiations that occur after establishment of the competitive range that may, at the Contracting Officer's discretion, result in the offeror being allowed to revise its proposal.

"In writing", *"writing"*, or *"written"* means any worded or numbered expression that can be read, reproduced, and later communicated, and includes electronically transmitted and stored information.

"*Proposal modification*" is a change made to a proposal before the solicitation's closing date and time, or made in response to an amendment, or made to correct a mistake at any time before award.

"*Proposal revision*" is a change to a proposal made after the solicitation closing date, at the request of or as allowed by a Contracting Officer as the result of negotiations.

"*Time,*" if stated as a number of days, is calculated using calendar days, unless otherwise specified, and will include Saturdays, Sundays, and legal holidays. However, if the last day falls on a Saturday, Sunday, or legal holiday, then the period shall include the next working day.

(b) *Amendments to solicitations*. If this solicitation is amended, all terms and conditions that are not amended remain unchanged. Offerors shall acknowledge receipt of any amendment to this solicitation by the date and time specified in the amendment(s).

(c) *Submission, modification, revision, and withdrawal of proposals*. (1) Unless other methods (*e.g.*, electronic commerce or facsimile) are permitted in the solicitation, proposals and modifications to proposals shall be submitted in paper media in sealed envelopes or packages (i) addressed to the office specified in the solicitation, and (ii) showing the time and date specified for receipt, the solicitation number, and the name and address of the offeror. Offerors using commercial carriers should ensure that the proposal is marked on the outermost wrapper with the information in paragraphs (c)(1)(i) and (c)(1)(ii) of this provision.

The first page of the proposal must show--
(i) The solicitation number;
(ii) The name, address, and telephone and facsimile numbers of the offeror (and electronic address if available);
(iii) A statement specifying the extent of agreement with all terms, conditions, and provisions included in the solicitation and agreement to furnish any or all items upon which prices are offered at the price set opposite each item;
(iv) Names, titles, and telephone and facsimile numbers (and electronic addresses if available) of persons authorized to negotiate on the offeror's behalf with the Government in connection with this solicitation; and
(v) Name, title, and signature of person authorized to sign the proposal. Proposals signed by an agent shall be accompanied by evidence of that agent's authority, unless that evidence has been previously furnished to the issuing office.

Submission, modification, revision, and withdrawal of proposals. (i) Offerors are responsible for submitting proposals, and any modifications or revisions, so as to reach the Government office designated in the solicitation by the time specified in the solicitation. If no time is specified in the solicitation, the time for receipt is 4:30 p.m., local time, for the designated Government office on the date that proposal or revision is due.
(ii) (A) Any proposal, modification, or revision received at the Government office designated in the solicitation after the exact time specified for receipt of offers is "late" and will not be

considered unless it is received before award is made, the Contracting Officer determines that accepting the late offer would not unduly delay the acquisition; and--

(*1*) If it was transmitted through an electronic commerce method authorized by the solicitation, it was received at the initial point of entry to the Government infrastructure not later than 5:00 p.m. one working day prior to the date specified for receipt of proposals; or

(*2*) There is acceptable evidence to establish that it was received at the Government installation designated for receipt of offers and was under the Government's control prior to the time set for receipt of offers; or

(*3*) It is the only proposal received.

(B) However, a late modification of an otherwise successful proposal that makes its terms more favorable to the Government, will be considered at any time it is received and may be accepted.

(iii) Acceptable evidence to establish the time of receipt at the Government installation includes the time/date stamp of that installation on the proposal wrapper, other documentary evidence of receipt maintained by the installation, or oral testimony or statements of Government personnel.

(iv) If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the office designated for receipt of proposals by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation, the time specified for receipt of proposals will be deemed to be extended to the same time of day specified in the solicitation on the first work day on which normal Government processes resume.

(v) Proposals may be withdrawn by written notice received at any time before award. Oral proposals in response to oral solicitations may be withdrawn orally. If the solicitation authorizes facsimile proposals, proposals may be withdrawn via facsimile received at any time before award, subject to the conditions specified in the provision at 52.215-5, Facsimile Proposals. Proposals may be withdrawn in person by an offeror or an authorized representative, if the identity of the person requesting withdrawal is established and the person signs a receipt for the proposal before award.

Unless otherwise specified in the solicitation, the offeror may propose to provide any item or combination of items.

Offerors shall submit proposals in response to this solicitation in English, unless otherwise permitted by the solicitation, and in U.S. dollars, unless the provision at FAR 52.225-17, Evaluation of Foreign Currency Offers, is included in the solicitation.

Offerors may submit modifications to their proposals at any time before the solicitation closing date and time, and may submit modifications in response to an amendment, or to correct a mistake at any time before award.

Offerors may submit revised proposals only if requested or allowed by the Contracting Officer.

Proposals may be withdrawn at any time before award. Withdrawals are effective upon receipt of notice by the Contracting Officer.

(d) *Offer expiration date*. Proposals in response to this solicitation will be valid for the number of days specified on the solicitation cover sheet (unless a different period is proposed by the offeror).

(e) *Restriction on disclosure and use of data*. (1) The proposal submitted in response to this request may contain data (trade secrets; business data, e.g., commercial information, financial information, and cost and pricing data; and technical data) which the offeror, including its prospective subcontractor(s), does not want used or disclosed for any purpose other than for evaluation of the proposal. The use and disclosure of any data may be so restricted; provided, that the Government determines that the data is not required to be

disclosed under the Freedom of Information Act, 5 U.S.C. 552, as amended, and the offeror marks the cover sheet of the proposal with the following statements, specifying the particular portions of the proposal which are to be restricted:

> Unless disclosure is required by the Freedom of Information Act, 5 U.S.C. 552, as amended, (the Act) as determined by Freedom of Information (FOI) officials of the Department of Health and Human Services, data contained in the portions of this proposal which have been specifically identified by page number, paragraph, etc. by the offeror as containing restricted information shall not be used or disclosed except for evaluation purposes.
>
> The offeror acknowledges that the Department may not be able to withhold a record (data, document, etc.) nor deny access to a record requested pursuant to the Act and that the Department's FOI officials must make that determination. The offeror hereby agrees that the Government is not liable for disclosure if the Department has determined that disclosure is required by the Act.
>
> If a contract is awarded to the offeror as a result of, or in connection with, the submission of this proposal, the Government shall have right to use or disclose the data to the extent provided in the contract. Proposals not resulting in a contract remain subject to the Act.
>
> The offeror also agrees that the Government is not liable for disclosure or use of unmarked data and may use or disclose the data for any purpose, including the release of the information pursuant to requests under the Act. The data subject to this restriction are contained in pages (*insert page numbers, paragraph designations, etc. or other identification*).

In addition, the offeror must mark each page of data it wishes to restrict with the following statement:

> "Use or disclosure of data contained on this page is subject to the restriction on the cover sheet of this proposal or quotation."

Offerors are cautioned that proposals submitted with restrictive statements or statements differing in substance from those cited above may not be considered for award. The Government reserves the right to reject any proposal submitted with a nonconforming statement(s).

(f) *Contract award*. (1) The Government intends to award a contract or contracts resulting from this solicitation to the responsible offeror(s) whose proposal(s) represents the best value after evaluation in accordance with the factors and subfactors in the solicitation.

(2) The Government may reject any or all proposals if such action is in the Government's interest.

(3) The Government may waive informalities and minor irregularities in proposals received.

(4) The Government intends to evaluate proposals and award a contract without discussions with offerors (except clarifications as described in FAR 15.306(a)). Therefore, the offeror's initial proposal should contain the offeror's best terms from a cost or price and technical standpoint. The Government reserves the right to conduct discussions if the Contracting Officer later determines them to be necessary. If the Contracting Officer determines that the number of proposals that would otherwise be in the competitive range exceeds the number at which an efficient competition can be conducted, the Contracting Officer may limit the number of proposals in the competitive range to the greatest number that will permit an efficient competition among the most highly rated proposals.

(5) The Government reserves the right to make an award on any item for a quantity less than the quantity offered, at the unit cost or prices offered, unless the offeror specifies otherwise in the proposal.

(6) The Government reserves the right to make multiple awards if, after considering the additional administrative costs, it is in the Government's best interest to do so.

(7) Exchanges with offerors after receipt of a proposal do not constitute a rejection or counteroffer by the Government.

(8) The Government may determine that a proposal is unacceptable if the prices proposed are materially unbalanced between line items or subline items. Unbalanced pricing exists when, despite an acceptable total evaluated price, the price of one or more contract line items is significantly overstated or understated as indicated by the application of cost or price analysis techniques. A proposal may be rejected if the Contracting Officer determines that the lack of balance poses an unacceptable risk to the Government.

(9) If a cost realism analysis is performed, cost realism may be considered by the source selection authority in evaluating performance or schedule risk.

(10) A written award or acceptance of proposal mailed or otherwise furnished to the successful offeror within the time specified in the proposal shall result in a binding contract without further action by either party.

(11) If a post-award debriefing is given to requesting offerors, the Government shall disclose the following information, if applicable:

(i) The agency's evaluation of the significant weak or deficient factors in the debriefed offeror's offer.
(ii) The overall evaluated cost or price and technical rating of the successful and debriefed offeror and past performance information on the debriefed offeror.
(iii) The overall ranking of all offerors, when any ranking was developed by the agency during source selection;
(iv) A summary of the rationale for award.
(v) For acquisitions of commercial items, the make and model of the item to be delivered by the successful offeror.
(vi) Reasonable responses to relevant questions posed by the debriefed offeror as to whether source-selection procedures set forth in the solicitation, applicable regulations, and other applicable authorities were followed by the agency.

(End of Provision)

Alternate I (October 1997). As prescribed in 15.209(a)(1), substitute the following paragraph (f)(4) for paragraph (f)(4) of the basic provision:

(f) (4) The Government intends to evaluate proposals and award a contract after conducting discussions with offerors whose proposals have been determined to be within the competitive range. If the Contracting Officer determines that the number of proposals that would otherwise be in the competitive range exceeds the number at which an efficient competition can be conducted, the Contracting Officer may limit the number of proposals in the competitive range to the greatest number that will permit an efficient competition among the most highly rated proposals. Therefore, the offeror's initial proposal should contain the offeror's best terms from a price and technical standpoint.

b. **NAICS CODE AND SIZE STANDARD**

Note: The following information is to be used by the offeror in preparing its Representations and Certifications (See Section K of this RFP), specifically in completing the provision entitled, SMALL BUSINESS PROGRAM REPRESENTATION, FAR Clause 52.219-1.

(1) The North American Industry Classification System (NAICS) code for this acquisition is 541710.

(2) The small business size standard is 500 employees.

THIS REQUIREMENT IS NOT SET-ASIDE FOR SMALL BUSINESS. However, the Federal Acquisition Regulation (FAR) requires in EVERY solicitation, (except for foreign acquisitions) the inclusion of the North American Industry Classification (NAICS) Code and corresponding size standard which best describes the nature of the requirement in the solicitation.

c. **TYPE OF CONTRACT AND NUMBER OF AWARDS**

It is anticipated that One Award will be made from this solicitation and that the award will be made on/about July 31, 2008.

It is anticipated that the award(s) from this solicitation will be a multiple-year cost reimbursement type contract completion with a term of six years, and that incremental funding will be used see, Section L.2.c., Business Proposal Instructions.

d. **ESTIMATE OF EFFORT**

It is expected that a completion type contract will be awarded as a result of this RFP. To assist you in the preparation of your proposal, the Government considers the effort to be approximately 25.5 labor hours for the base period and 9 labor hours for the options. This information is furnished for the offeror's information only and is not to be considered restrictive for proposal purposes.

e. **COMMITMENT OF PUBLIC FUNDS**

The Contracting Officer is the only individual who can legally commit the Government to the expenditure of public funds in connection with the proposed procurement. Any other commitment, either explicit or implied, is invalid.

f. **COMMUNICATIONS PRIOR TO CONTRACT AWARD**

Offerors shall direct all communications to the attention of the Contract Specialist or Contracting Officer cited on the face page of this RFP. Communications with other officials may compromise the competitiveness of this acquisition and result in cancellation of the requirement.

g. **RELEASE OF INFORMATION**

Contract selection and award information will be disclosed to offerors in accordance with regulations applicable to negotiated acquisition. Prompt written notice will be given to unsuccessful offerors as they are eliminated from the competition, and to all offerors following award.

h. **COMPARATIVE IMPORTANCE OF PROPOSALS**

You are advised that paramount consideration shall be given to the evaluation of technical proposals. All evaluation factors other than cost or price, when combined, are significantly more important than cost or price. The relative importance of the evaluation factors are specified in SECTION M of this solicitation. However, the Government reserves the right to make an award to the best advantage of the Government, cost and other factors considered.

i. **PREPARATION COSTS**

This RFP does not commit the Government to pay for the preparation and submission of a proposal.

j. **SERVICE OF PROTEST** (SEPTEMBER 2006) - FAR 52.233-2

(a) Protests, as defined in section 33.101 of the Federal Acquisition Regulation, that are filed directly with an agency, and copies of any protests that are filed with the Government Accountability Office (GAO), shall be served on the Contracting Officer (addressed as follows) by obtaining written and dated acknowledgment of receipt from:

Contracting Officer
Office of Acquisitions
National Institute of Allergy and Infectious Diseases
Room 3214
6700-B Rockledge Drive
BETHESDA MD 20892-7612

(b) The copy of any protest shall be received in the office designated above within one day of filing a protest with the GAO.

(End of Provision)

k. **LATE PROPOSALS AND REVISIONS**, HHSAR 352.215-70 (January 2006)

Notwithstanding the procedures contained in FAR 52.215-1(c)(3) of the provision of this solicitation entitled Instructions to Offerors-Competitive Acquisition, a proposal received after the date specified for receipt may be considered if it appears to offer the best value to the Government; and it was received before proposals were distributed for evaluation, or within five calendar days after the exact time specified for receipt, whichever is earlier.

(End of provision)

2. INSTRUCTIONS TO OFFERORS

a. GENERAL INSTRUCTIONS

INTRODUCTION

The following instructions will establish the acceptable minimum requirements for the format and contents of proposals. Special attention is directed to the requirements for technical and business proposals to be submitted in accordance with these instructions.

(1) **Contract Type and General Clauses**

It is contemplated that a cost-reimbursement completion type contract will be awarded. (See General Information) Any resultant contract shall include the clauses applicable to the selected offeror's organization and type of contract awarded as required by Public Law, Executive Order, or acquisition regulations in effect at the time of execution of the proposed contract.

(2) **Authorized Official and Submission of Proposal**

The proposal must be signed by an official authorized to bind your organization and must stipulate that it is predicated upon all the terms and conditions of this RFP. Your proposal shall be submitted in the number of copies, to the addresses, and marked as indicated in the Attachment entitled, PACKAGING AND DELIVERY OF PROPOSAL, Part III, Section J hereof. Proposals will be typewritten, paginated, reproduced on letter size paper and will be legible in all required copies. To expedite the proposal evaluation, all documents required for responding to the RFP should be placed in the following order:

I. COVER PAGE

Include RFP title, number, name of organization, DUNS No., identification of the proposal part, and indicate whether the proposal is an original or a copy.

II. TECHNICAL PROPOSAL

It is recommended that the technical proposal consist of a cover page, a table of contents, and the information requested in the Technical Proposal Instructions and as specified in SECTION J, List of Attachments.

III. BUSINESS PROPOSAL

It is recommended that the business proposal consist of a cover page, a table of contents, and the information requested in the Business Proposal Instructions and as specified in SECTION J, List of Attachments.

(3) **Proposal Summary and Data Record (NIH-2043)**

The Offeror must complete the Form NIH-2043, attached, with particular attention to the length of time the proposal is firm and the designation of those personnel authorized to conduct negotiations. (See Section J, Attachment entitled, PROPOSAL SUMMARY AND DATA RECORD.)

(4) **Separation of Technical and Business Proposals**

The proposal must be prepared in two parts: a "Technical Proposal" and a "Business Proposal." Each of the parts shall be separate and complete in itself so that evaluation of one may be accomplished independently of, and concurrently with, evaluation of the other. The technical proposal must include direct cost and resources information, such as labor-hours and categories and applicable rates, materials, subcontracts, travel, etc., and associated costs so that the offeror's understanding of the project may be evaluated (See Attachment entitled, TECHNICAL PROPOSAL COST SUMMARY). However, the technical proposal should **not** include pricing data relating to individual salary information, indirect cost rates or

amounts, fee amounts (if any), and total costs. The technical proposal should disclose your technical approach in as much detail as possible, including, but not limited to, the requirements of the technical proposal instructions.

(5) **Alternate Proposals**

You may, at your discretion, submit alternate proposals, or proposals which deviate from the requirements; provided, that you also submit a proposal for performance of the work as specified in the statement of work. Such proposals may be considered if overall performance would be improved or not compromised and if they are in the best interests of the Government. Alternative proposals, or deviations from any requirements of this RFP, shall be clearly identified.

(6) **Evaluation of Proposals**

The Government will evaluate technical proposals in accordance with the criteria set forth in Part IV, Section M of this RFP.

(7) **Potential Award Without Discussions**

The Government reserves the right to award a contract without discussions if the Contracting Officer determines that the initial prices are fair and reasonable and that discussions are not necessary.

(8) **Use of the Metric System of Measurement**

It is the policy of the Department of Health and Human Services to support the Federal transition to the metric system and to use the metric system of measurement in all procurement, grants, and other business related activities unless such use is impracticable or is likely to cause significant inefficiencies.

The offeror is encouraged to prepare their proposal using either "Hard Metric," "Soft Metric," or "Dual Systems" of measurement. The following definitions are provided for your information:

Hard Metric - The replacement of a standard inch-pound size with an accepted metric size for a particular purpose. An example of size substitution might be: selling or packaging liquids by the liter instead of by the pint or quart (as for soft drinks), or instead of by the gallon (as for gasoline).

Soft Metric - The result of a mathematical conversion of inch-pound measurements to metric equivalents for a particular purpose. The physical characteristics are not changed.

Dual Systems - The use of both inch-pound and metric systems. For example, an item is designed, produced, and described in inch-pound values with soft metric values also shown for information or comparison purposes.

(9) **Standards for Privacy of Individually Identifiable Health Information**

The Department of Health and Human Services (DHHS) issued final modifications to the “Standards for Privacy of Individually Identifiable Health Information,” the “Privacy Rule,” on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as “covered entities” must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply.

Decisions about the applicability and implementation of the Privacy Rule reside with the contractor and his/her institution. The OCR Web site (http://www.hhs.gov/ocr/) provides information of the Privacy Rule, including a complete Regulation Text and a set of decision tools on “Am I a covered entity?” Information

on the impact of the HIPAA Privacy Rule on NIH processes involving the review, award, and administration of grants, cooperative agreements and contracts can be found at: http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

(10) **Specific Copyright Provisions Applicable to Software Development and/or Enhancement(s)**

Under the provisions of the Rights in Data General clause (52.227-14), contractors must seek permission to establish a copyright for software and associated data generated under a contract. As a general rule, permission is normally granted provided, a paid-up, world-wide, irrevocable, nonexclusive license to the government is provided. This is to advise offerors that for this project, the government intends to assert additional copyright permissions under this contract.

(11) **Privacy Act - Treatment of Proposal Information**

The Privacy Act of 1974 (P.L. 93-579) requires that a Federal agency advise each individual whom it asks to supply information, the authority which authorizes the solicitation, whether disclosure is voluntary or mandatory, the principal purpose or purposes for which the information is intended to be used, the uses outside the agency which may be made of the information, and the effects on the individual, if any, of not providing all or any part of the requested information.

The NIH is requesting the information called for in this RFP pursuant to the authority provided by Sec. 301(a)(7) of the Public Health Service Act, as amended, and P.L. 92-218, as amended.

Providing the information requested is entirely voluntary. The collection of this information is for the purpose of conducting an accurate, fair, and adequate review prior to a discussion as to whether to award a contract.

Failure to provide any or all of the requested information may result in a less than adequate review.

In addition, the Privacy Act of 1974 (P.L. 93-579, Section 7) requires that the following information be provided when individuals are requested to disclose their social security number.

Provision of the social security number is voluntary. Social security numbers are requested for the purpose of accurate and efficient identification, referral, review and management of NIH contracting programs. Authority for requesting this information is provided by Section 301 and Title IV of the PHS Act, as amended.

The information provided by you may be routinely disclosed for the following purposes:

- to the cognizant audit agency and the General Accounting Office for auditing.
- to the Department of Justice as required for litigation.
- to respond to congressional inquiries.
- to qualified experts, not within the definition of Department employees, for opinions as a part of the review process.

(12) **Selection of Offerors**

a) The acceptability of the scientific and technical portion of each research contract proposal will be evaluated by a technical review committee. The committee will evaluate each proposal in strict conformity with the evaluation criteria of the RFP, utilizing point scores and written critiques. The committee may suggest that the Contracting Officer request clarifying information from an offeror.

b) The business portion of each contract proposal will be subjected to a cost and price analysis, management analysis, etc.

c) If award will be made without conducting discussions, offerors may be given the opportunity to clarify

certain aspects of their proposal (e.g., the relevance of an offeror's past performance information and adverse past performance information to which the offeror has not previously had an opportunity to respond) or to resolve minor or clerical errors.

d) If the Government intends to conduct discussions prior to awarding a contract-

(1) Communications will be held with offerors whose past performance information is the determining factor preventing them from being placed within the competitive range. Such communications shall address adverse past performance information to which an offeror has not had a prior opportunity to respond. Also, communications may be held with any other offerors whose exclusion from, or inclusion in, the competitive range is uncertain.

Such communications shall not be used to cure proposal deficiencies or omissions that alter the technical or cost elements of the proposal, and/or otherwise revise the proposal, but may be considered in rating proposals for the purpose of establishing the competitive range.

(2) The Contracting Officer will, in concert with program staff, decide which proposals are in the competitive range. The competitive range will be comprised of all of the most highly rated proposals. Oral or written discussions will be conducted with all offerors in the competitive range.

While it is NIAID's policy to conduct discussions with all offerors in the competitive range, NIAID reserves the right, in special circumstances, to limit the number of proposals included in the competitive range to the greatest number that will permit an efficient competition. All aspects of the proposals are subject to discussions, including cost, technical approach, past performance, and contractual terms and conditions. At the conclusion of discussions, each offeror still in the competitive range shall be given an opportunity to submit a written Final Proposal Revision (FPR) with the reservation of the right to conduct finalization of details with the selected source in accordance with HHSAR 315.370.

e) The process described in FAR 15.101-1 will be employed, which permits the Government to make tradeoffs among cost or price and non-cost factors and to consider award to other than the lowest price offeror or other than the highest technically rated offeror. This process will take into consideration the results of the technical evaluation, the past performance evaluation, and the cost analysis.

f) The NIAID reserves the right to make a single award, multiple awards, or no award at all to the RFP. In addition, the RFP may be amended or canceled as necessary to meet NIAID requirements. Synopses of awards exceeding $25,000 will be published in FedBizOpps.

(13) **Institutional Responsibility Regarding Conflicting Interests of Investigators**

EACH INSTITUTION MUST:

(a) Maintain an appropriate written, enforced policy on conflict of interest that complies with 42 CFR Part 50 Subpart F and/or 45 CFR Part 94 as appropriate and inform each investigator of the Institution's policy, the Investigator's reporting responsibilities, and the applicable regulations. If the Institution carries out the NIH funded research through subgrantees, contractors or collaborators, the Institution must take reasonable steps to ensure that Investigators working for such entities comply with the regulations, either by requiring those investigators to comply with the Institution's policy or by requiring the entities to provide assurances to the Institution that will enable the Institution to comply with the regulations.

(b) Designate an Institutional official(s) to solicit and review financial disclosure statements from each Investigator who is planning to participate in NIH-funded research.

(c) Require that by the time an application/proposal is submitted to the NIH each investigator who is planning to participate in the NIH-funded research has submitted to the designated official(s) a listing

of his/her known Significant Financial Interests (and those of his/her spouse and dependent children): (i) that would reasonably appear to be affected by the research for which the NIH funding is sought; and (ii) in entities whose financial interests would reasonably appear to be affected by the research. All financial disclosures must be updated during the period of the award, either on an annual basis or as new reportable Significant Financial Interests are obtained.

(d) Provide guidelines consistent with the regulations for the designated official(s) to identify conflicting interests and take such actions as necessary to ensure that such conflicting interests will be managed, reduced, or eliminated.

(e) Maintain records, identifiable to each award, of all financial disclosures and all actions taken by the institution with respect to each conflicting interest for: (1) in the case of grants, at least three years from the date of submission of the final expenditures report or, where applicable, from other dates specified in 45 CFR Part 74.53(b) and (2) in the case of contracts, 3 years after final payment or, where applicable, for the other time period specified in 48 CFR Part 4 Subpart 4.7, Contract Records Retention.

(f) Establish adequate enforcement mechanisms and provide for sanctions where appropriate.

(g) Certify, in each application/proposal for funding to which the regulations applies, that:

1) there is in effect at the Institution a written and enforced administrative process to identify and manage, reduce or eliminate conflicting interests with respect to all research projects for which funding is sought from the NIH;

2) prior to the Institution's expenditure of any funds under the award, the Institution will report to the awarding component the existence of a conflicting interest (but not the nature of the interest or other details) found by the Institution and assure that the interest has been managed, reduced or eliminated in accord with the regulations; and for any interest that the Institution identifies as conflicting subsequent to the expenditure of funds after award, the report will be made and the conflicting interest managed, reduced, or eliminated, at least on a temporary basis within sixty days of that identification;

3) the Institution agrees to make information available, upon request, to the awarding component regarding all conflicting interests identified by the Institution and how those interested have been managed, reduced, or eliminated to protect the research from bias; and

4) the Institution will otherwise comply with the regulations.

Institutional Management of Conflicting Interests

(a) The designated official(s) must: (1) review all financial disclosures; and (2) determine whether conflict of interest exists, and if so, determine what actions should be taken by the Institution to manage, reduce or eliminate such conflict of interest. **A conflict of interest exists when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the NIH-funded research**.

Examples of conditions or restrictions that might be imposed to manage actual or potential conflicts of interests include, but are not limited to:

(i) public disclosure of significant financial interests;
(ii) monitoring of research by independent reviewers;
(iii) modification of the research plan;
(iv) disqualification of the Investigator(s) from participation in all or a portion of the research funded by the awarding component;
(v) divestiture of significant financial interests; or
(vi) severance of relationships that create actual or potential conflicts of interests.

(b) An Institution may require the management of other conflicting financial interests in addition to those

described in paragraph (a) of this section, as the Institution deems appropriate.

(14) **ROTC Access and Federal Military Recruiting on Campus**

Section 514 of the FY 1997 Appropriations Act prohibits NIH from providing contract funds to educational institutions that the Secretary of Defense determines have a policy or practice (regardless of when implemented) that either prohibits, or in effect prevents (1) the maintaining, establishing, or operation of a unit of the Senior Reserve Officer Training Corps at the covered education entity; or (2) a student at the covered educational entity from enrolling in a unit of the Senior Reserve Officer Training Corps at another institution of higher education.

Further, contract funds may not be provided to educational institutions that have a policy or practice that prohibits or prevents (1) entry to campuses, or access to students (who are 17 years of age or older) on campuses, for purposes of Federal military recruiting; or (2) access by military recruiters for purposes of Federal military recruiting to information pertaining to students (who are 17 years of age or older) enrolled at the covered educational entity.

(15) **Past Performance Information**

a) Offerors shall submit the following information as part of their business proposal.

A list of the last five (5) contracts completed during the past three (3) years and the last three (3) contracts currently being performed that are similar in nature to the solicitation workscope. Contracts listed may include those entered into by the Federal Government, agencies of state and local governments and commercial concerns. Offerors may also submit past performance information regarding predecessor companies, key personnel who have relevant experience or subcontractors that will perform major or critical aspects of the requirement when such information is relevant to the instant acquisition. For the purposes of this solicitation, a "major subcontract" is defined as any subcontract over $550,000.

Include the following information for each contract or subcontract listed:

1. Name of Contracting Organization
2. Contract Number (for subcontracts, provide the prime contract number and the subcontract number)
3. Contract Type
4. Total Contract Value
5. Description of Requirement
6. Contracting Officer's Name and Telephone Number
7. Program Manager's Name and Telephone Number
8. Standard Industrial Code

The offeror may provide information on problems encountered on the identified contracts and the offeror's corrective actions.

b) The Government is not required to contact all references provided by the offeror. Also, references other than those identified by the offeror may be contacted by the Government to obtain additional information that will be used in the evaluation of the offeror's past performance.

(16) **Electronic and Information Technology Accessibility HHSAR 352.270-19(a) (January 2006)**

Section 508 of the Rehabilitation Act of 1973 (29 U.S.C. 794d), as amended by Public Law 105–220 under Title IV (Rehabilitation Act Amendments of 1998) and the Architectural and Transportation Barriers Compliance Board Electronic and Information (EIT) Accessibility Standards (36 CFR part 1194), require that all EIT acquired must ensure that::

a. Federal employees with disabilities have access to and use of information and data that is

comparable to the access and use by Federal employees who are not individuals with disabilities; and

b. Members of the public with disabilities seeking information or services from an agency have access to and use of information and data that is comparable to the access to and use of information and data by members of the public who are not individuals with disabilities.

This requirement includes the development, procurement, maintenance, and/or use of EIT products/services; therefore, any proposal submitted in response to this solicitation must demonstrate compliance with the established EIT Accessibility Standards. Information about Section 508 is available at http://www.section508.gov/.

(End of provision)

(17) **Prohibition on Contractor Involvement with Terrorist Activities**

The contractor acknowledges that U.S. Executive Orders and Laws, including but not limited to E.O. 13224 and P.L. 107-56, prohibit transactions with, and the provision of resources and support to, individuals and organizations associated with terrorism. It is the legal responsibility of the contractor to ensure compliance with these Executive Orders and Laws. This clause must be included in all subcontracts issued under this contract.

(18) **Solicitation Provisions Incorporated by Reference, FAR 52.252-1 (February 1998)**

This Solicitation incorporates one or more solicitation provisions by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available. The offeror is cautioned that the listed provisions may include blocks that must be completed by the offeror and submitted with its quotation or offer. In lieu of submitting the full text provisions, the offeror may identify the provision by paragraph identifier and provide the appropriate information with its quotation or offer. Also, the full text of a solicitation provision may be accessed electronically at this address: http://www.acquisition.gov/far/index.html.

FEDERAL ACQUISITION REGULATION (48 CFR CHAPTER 1):

a) Data Universal Numbering System (DUNS) Number, FAR Clause 52.204-6 (October 2003).

b) Submission of Offers in the English Language, FAR Clause 52.214-34, (April 1991).

c) Submission of Offers in U.S. Currency, FAR Clause 52.214-35, (April 1991).

d) Facilities Capital Cost of Money, FAR Clause 52.215-16, (October 1997).

e) Order of Precedence-Uniform Contract Format, FAR Clause 52.215-8, (October 1997).

f) Preaward On-Site Equal Opportunity Compliance Evaluation, (Over $10,000,000), FAR Clause 52.222-24, (February 1999).

b. TECHNICAL PROPOSAL INSTRUCTIONS

A detailed work plan must be submitted indicating how each aspect of the statement of work is to be accomplished. Your technical approach should be in as much detail as you consider necessary to fully explain your proposed technical approach or method. The technical proposal should reflect a clear understanding of the nature of the work being undertaken. The technical proposal must include information on how the project is to be organized, staffed, and managed. Information should be provided which will demonstrate your understanding and management of important events or tasks.

(1) **Technical Discussions**

The technical discussion included in the technical proposal should respond to the items set forth below:

a) **Project Objectives, NIH-1688-1**

The offeror shall insert a completed NIH Form 1688-1, Project Objective, as provided in Section J, Attachments, behind the Title Page of each copy of the proposal, along with the "Government Notice for Handling Proposals." The NIH Form 1688-1 is to be completed as follows:

- For an **Institution of Higher Education:** The form MUST be completed in its entirety.
- For **OTHER** than an Institution of Higher Education: The starred items (Department, Service, Laboratory or Equivalent, and Major Subdivision) should be left blank.

The information required under the "Summary of Objectives" portion of the form MUST meet the requirements set forth in the section of the form entitled, **"INSTRUCTIONS:"**

b) **Statement of Work**

(1) Objectives

State the overall objectives and the specific accomplishments you hope to achieve. Indicate the rationale for your plan, and relation to comparable work in progress elsewhere. Review pertinent work already published which is relevant to this project and your proposed approach. This should support the scope of the project as you perceive it.

(2) Approach

Use as many subparagraphs, appropriately titled, as needed to clearly outline the general plan of work. Discuss phasing of research and, if appropriate, include experimental design and possible or probable outcome of approaches proposed.

(3) Methods

Describe in detail the methodologies you will use for the project, indicating your level of experience with each, areas of anticipated difficulties, and any unusual expenses you anticipate.

(4) Schedule

Provide a schedule for completion of the work and delivery of items specified in the statement of work. Performance or delivery schedules shall be indicated for phases or segments, as applicable, as well as for the overall program. Schedules shall be shown in terms of calendar months from the date of authorization to proceed or, where applicable, from the date of a stated event, as for example, receipt of a required approval by the Contracting Officer. Unless the request for proposal indicates that the stipulated schedules are mandatory, they shall be treated as desired or recommended schedules. In this event, proposals based upon the offeror's best alternative schedule, involving no overtime, extra shift or other premium, will be accepted for consideration.

c) **Personnel**

Describe the experience and qualifications of personnel who will be assigned for direct work on this program. Information is required which will show the composition of the task or work group, its general qualifications, and recent experience with similar equipment or programs. Special mention shall be made of direct technical supervisors and key technical personnel, and the approximate percentage of the total time each will be available for this program.

OFFERORS SHOULD ASSURE THAT THE PRINCIPAL INVESTIGATOR, AND ALL OTHER PERSONNEL PROPOSED, SHALL NOT BE COMMITTED ON FEDERAL GRANTS AND CONTRACTS FOR MORE THAN A TOTAL OF 100% OF THEIR TIME. IF THE SITUATION ARISES WHERE IT IS DETERMINED THAT A PROPOSED EMPLOYEE IS COMMITTED FOR MORE THAN 100% OF HIS OR HER TIME, THE GOVERNMENT WILL REQUIRE ACTION ON THE PART OF THE OFFEROR TO CORRECT THE TIME COMMITMENT.

(1) Single Principal Investigator/Project Director

List the name of the Principal Investigator/Project Director responsible for overall implementation of the contract and key contact for technical aspects of the project. Even though there may be co-investigators, identify the Principal Investigator/Project Director who will be responsible for the overall implementation of any awarded contract. Discuss the qualifications, experience, and accomplishments of the Principal Investigator/Project Director. State the estimated time to be spent on the project, his/her proposed duties, and the areas or phases for which he/she will be responsible.

(2) Other Investigators

List all other investigators/professional personnel who will be participating in the project. Discuss the qualifications, experience, and accomplishments. State the estimated time each will spend on the project, proposed duties on the project, and the areas or phases for which each will be responsible.

(3) Additional Personnel

List names, titles, and proposed duties of additional personnel, if any, who will be required for full-time employment, or on a subcontract or consultant basis. The technical areas, character, and extent of subcontract or consultant activity will be indicated and the anticipated sources will be specified and qualified. For all proposed personnel who are not currently members of the offeror's staff, a letter of commitment or other evidence of availability is required. A resume does not meet this requirement. Commitment letters for use of consultants and other personnel to be hired must include:

-The specific items or expertise they will provide.

-Their availability to the project and the amount of time anticipated.

-Willingness to act as a consultant.

-How rights to publications and patents will be handled.

(4) Resumes

Resumes of all key personnel are required. Each must indicate educational background, recent experience, specific or technical accomplishments, and a listing of relevant publications.

(2) **Technical Evaluation**

Proposals will be technically evaluated in accordance with the factors, weights, and order of relative importance as described in SECTION M - Evaluation Factors for Award of this solicitation.

(3) **Additional Technical Proposal Information**

a) Proposals which merely offer to conduct a program in accordance with the requirements of the Government's scope of work will not be eligible for award. The offeror must submit an explanation of the proposed technical approach in conjunction with the tasks to be performed in achieving the project objectives.

b) The technical evaluation is conducted in accordance with the weighted technical evaluation criteria by an initial review panel. This evaluation produces a numerical score (points) which is based upon the information contained in the offeror's proposal only.

(4) **Other Considerations**

Record and discuss specific factors not included elsewhere which support your proposal. Using specifically titled subparagraphs, items may include:

a) Any agreements and/or arrangements with subcontractor(s). Provide as much detail as necessary to explain how the statement of work will be accomplished within this working relationship.

b) Unique arrangements, equipment, etc., which none or very few organizations are likely to have which is advantageous for effective implementation of this project.

c) Equipment and unusual operating procedures established to protect personnel from hazards associated with this project.

d) Other factors you feel are important and support your proposed research.

e) Recommendations for changing reporting requirements if such changes would be more compatible with the offeror's proposed schedules.

(5) **Obtaining and Disseminating Biomedical Research Resources**

As a public sponsor of biomedical research, the National Institutes of Health (NIH) has a dual interest in accelerating scientific discovery and facilitating product development. Intellectual property restrictions can stifle the broad dissemination of new discoveries and limit future avenues of research and product development. At the same time, reasonable restrictions on the dissemination of research tools are sometimes necessary to protect legitimate proprietary interests and to preserve incentives for commercial development. To assist NIH contractors achieve an appropriate balance, the NIH has provided guidance in the form of a two-part document, consisting of Principles setting forth the fundamental concepts and Guidelines that provide specific information to patent and license professionals and sponsored research administrators for implementation.

The purpose of these Principles and Guidelines is to assist NIH funding recipients in determining: 1) Reasonable terms and conditions for making NIH-funded research resources available to scientists in other institutions in the public and private sectors (disseminating research tools); and 2) Restrictions to accept as a condition of receiving access to research tools for use in NIH-funded research (acquiring research tools). The intent is to help recipients ensure that the conditions they impose and accept on the transfer of research tools will facilitate further biomedical research, consistent with the requirements of the Bayh-Dole Act and NIH funding policy.

This policy, entitled, "Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts," (Federal Register Notice, December 23, 1999 [64 FR 72090] will be included in any contract awarded from this solicitation. It can be found at the following website: http://ott.od.nih.gov/NewPages/64FR72090.pdf.

(a) **Sharing Research Data**

The NIH endorses the sharing of final research data to expedite the translation of research results into knowledge, products, and procedures to improve human health. This contract is expected to generate research data. Therefore, the offeror must submit a plan in its technical proposal for data sharing or state why data sharing is not possible. If data sharing is limited, the offeror should explain such limitations in its data sharing plan. NIH's data sharing policy may be found at the following Web site:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html

If the resultant contract is part of a collaborative program involving multiple sites, the data sharing will be governed by a dissemination plan to be developed jointly following award. Offerors must include in their proposals a statement of willingness to work collaboratively after award with the other funded sites to prepare a joint dissemination plan. Coordinating Center proposals should describe methods to coordinate the dissemination planning and implementation. The Coordinating Center must include a budget and justification for any additional costs of this collaborative effort.

(6) **Information Security** is applicable to this solicitation and the following information is provided to assist in proposal preparation.

IMPORTANT NOTE TO OFFERORS: The following information shall be addressed in a separate section of the Technical Proposal entitled, "INFORMATION SECURITY."

The Federal Information Security Management Act of 2002 (P.L. 107-347) (FISMA) requires each agency to develop, document, and implement an agency-wide information security program to safeguard information and information systems that support the operations and assets of the agency, including those provided or managed by another agency, contractor (including subcontractor), or other source. The National Institute of Standards and Technology (NIST) has issued a number of publications that provide guidance in the establishment of minimum security controls for management, operational and technical safeguards needed to protect the confidentiality, integrity and availability of a Federal information system and its information.

The Statement of Work (SOW) requires the successful offeror to (1) develop, (2) have the ability to access, or (3) host and/or maintain a Federal information system(s). Pursuant to Federal and HHS Information Security Program Policies the following requirements apply to this solicitation:

Federal Information Security Management Act of 2002 (FISMA), Title III, E-Government Act of 2002, Pub. L. No. 107-347 (Dec. 17, 2002); http://csrc.nist.gov/policies/FISMA-final.pdf

(a) Information Type

[ ] Administrative, Management and Support Information:

[X] Mission Based Information:

(b) Security Categories and Levels

Confidentiality	Level:	**[ ]** Low	**[X]** Moderate	**[ ]** High
Integrity	Level:	**[ ]** Low	**[X]** Moderate	**[ ]** High
Availability	Level:	**[ ]** Low	**[X]** Moderate	**[ ]** High
Overall	**Level:**	**[ ] Low**	**[X] Moderate**	**[ ] High**

(c) Position Sensitivity Designations

Prior to award, the Government will determine the position sensitivity designation for each contractor (including subcontractor) employee that the successful offeror proposes for work under the contract. For proposal preparation purposes, the following designations apply:

[ ] **Level 6: Public Trust - High Risk (Requires Suitability Determination with a BI)**. Contractor employees assigned to a Level 6 position are subject to a Background Investigation (BI).

[X] **Level 5: Public Trust - Moderate Risk (Requires Suitability Determination with NACIC, MBI or LBI)**. Contractor employees assigned to a Level 5 position with no previous investigation and approval shall undergo a National Agency Check and Inquiry Investigation plus a Credit Check (NACIC), a Minimum Background Investigation (MBI), or a Limited Background Investigation (LBI).

[ ] **Level 1: Non Sensitive (Requires Suitability Determination with an NACI)**. Contractor employees assigned to a Level 1 position are subject to a National Agency Check and Inquiry Investigation (NACI).

Upon award, the contractor will be required to submit a roster of all staff (including subcontractor staff) working under the contract who will develop, have the ability to access, or host and/or maintain a federal information system(s). The Government will determine and notify the Contractor of the appropriate level of suitability investigation required for each staff member. An electronic template, "Roster of Employees Requiring Suitability Investigations," is available for contractor use at: http://ais.nci.nih.gov/forms/Suitability-roster.xls

Upon receipt of the Government's notification of applicable Suitability Investigations required, the contractor shall complete and submit the required forms within 30 days of the notification. Additional submission instructions can be found at the "NCI Information Technology Security Policies, Background Investigation Process" website: http://ais.nci.nih.gov.

Contractor/subcontractor employees who have met investigative requirements within the past five years may only require an updated or upgraded investigation.

(d) Information Security Training

HHS policy requires contractors/subcontractors receive security training commensurate with their responsibilities for performing work under the terms and conditions of their contractual agreements.

The successful offeror will be responsible for assuring that each contractor/subcontractor employee has completed the NIH Computer Security Awareness Training course at: [insert link for course] prior to performing any contract work, and thereafter completing the NIH-specified fiscal year refresher course during the period of performance of the contract. The successful offeror shall maintain a listing of all individuals who have completed this training and shall submit this listing to the Project Officer. Additional security training requirements commensurate with the position may be required as defined in NIST Special Publication 800-16, Information Technology Security Training Requirements (http://csrc.nist.gov/publications/nistpubs/800-16/800-16.pdf). This document provides information about information security training that may be useful to potential offerors.

(e) Offeror's Official Responsible for Information Security

The offeror shall include in the "Information Security" part of its Technical Proposal the name and title of its official who will be responsible for all information security requirements should the offeror be selected for an award.

(f) NIST SP 800-26 Self-Assessment Questionnaire

The offeror must include in the "Information Security" part of its Technical Proposal, a completed Self-Assessment Questionnaire required by NIST Draft SP 800-26, Revision 1, Guide for Information Security Program Assessments and System Reporting Form at: (http://csrc.nist.gov/publications/drafts/Draft-sp800-26Rev1.pdf, See Appendix B for submission format.) NIST 800-26 assesses information security assurance of the offeror's internal systems security. This assessment is based on the Federal IT Security Assessment Framework and Draft NIST SP 800-53, Revision 1, Recommended Security Controls for Federal Information Systems, at: (http://www.csrc.nist.gov/publications/drafts/800-53-rev1-clean-sz.pdf).

Subcontracts: The offeror must include similar information for any proposed subcontractor that will perform under the SOW to (1) develop a Federal information system(s) at the offeror's/subcontractor's facility, or (2) host and/or maintain a Federal information system(s) at the offeror's/subcontractor's facility.

(g) Draft Information System Security Plan

The offeror must include a draft Information System Security Plan (ISSP) using the current template in Appendix A of NIST SP 800-18, Guide to Developing Security Plans for Federal Information Systems (http://csrc.nist.gov/publications/nistpubs/800-18-Rev1/sp800-18-Rev1-final.pdf). The details contained in the offeror's draft ISSP must be commensurate with the size and complexity of the requirements of the SOW based on the System Categorization determined above in subparagraph (b) Security Categories and Levels.

Subcontracts: The offeror must include similar information for any proposed subcontractor that will perform under the SOW with the offeror whenever the submission of an ISSP is required.

Note to Offeror: The resultant contract will require the draft ISSP to be finalized in coordination with the Project Officer no later than 90 calendar days after contract award. Also, a contractor is required to update and resubmit its ISSP to NIH every three years following award or when a major modification has been made to its internal system.

(i) References

(1) Federal Information Security Management Act of 2002 (FISMA), Title III, E-Government Act of 2002, Pub. L. No. 107-347 (Dec. 17, 2002); http://csrc.nist.gov/policies/FISMA-final.pdf
(2) DHHS Personnel Security/Suitability Handbook: http://www.hhs.gov/ohr/manual/pssh.pdf
(3) NIH Computer Security Awareness Training Course: http://irtsectraining.nih.gov/

The following NIST publications may be found at the following site: http://csrc.nist.gov/publications/
[Note: The search tool on the left side of this page provides easy access to the documents.]

(4) NIST Special Publication 800-16, Information Technology Security Training Requirements; and Appendix A-D
(5) NIST SP 800-18, Guide for Developing Security Plans for Information Technology Systems
(6) NIST SP 800-26, Revision 1, Computer Security
(7) NIST SP 800-53, Revision 1, Recommended Security Controls for Federal Information Systems
(8) NIST SP 800-60, Guide for Mapping Types of Information and Information Systems to Security Categories, Volume I; and
Volume II, Appendices to Guide For Mapping Types of Information and Information Systems To Security Categories, Appendix C, and Appendix D
(9) NIST SP 800-64, Security Considerations in the Information System Development Life Cycle
(10) FIPS PUB 199, Standards for Security Categorization of Federal Information and Information Systems
(11) FIPS PUB 200, Minimum Security Requirements for Federal Information and Information Systems

c. BUSINESS PROPOSAL INSTRUCTIONS

(1) Basic Cost/Price Information

The business proposal must contain sufficient information to allow the Government to perform a basic analysis of the proposed cost or price of the work. This information shall include the amounts of the basic elements of the proposed cost or price. These elements will include, as applicable, direct labor, fringe benefits, travel, materials, subcontracts, purchased parts, shipping, indirect costs and rate, fee, and profit.

(2) Proposal Cover Sheet

The following information shall be provided on the first page of your pricing proposal:

1. Solicitation, contract, and/or modification number;
2. Name and address of Offeror;
3. Name and telephone number of point of contact;
4. Name, address, and telephone number of Contract Administration Office, (if available);
5. Name, address, and telephone number of Audit Office (if available);
6. Proposed cost and/or price; profit or fee (as applicable); and total;
7. The following statement: By submitting this proposal, the offeror, if selected for discussions, grants the contracting officer or an authorized representative the right to examine, at any time before award, any of those books, records, documents, or other records directly pertinent to the information requested or submitted.
8. Date of submission; and
9. Name, title and signature of authorized representative.

This cover sheet information is for use by offerors to submit information to the Government when cost or pricing data are not required but information to help establish price reasonableness or cost realism is necessary. Such information is not considered cost or pricing data, and shall not be certified in accordance with FAR 15.406-2.

(3) Information Other than Cost or Pricing Data

a) The information submitted shall consist of data to permit the Contracting Officer and authorized representatives to determine price reasonableness or cost realism, e.g., information to support an analysis of material costs (when sufficient information on labor and overhead rates is already available), or information on prices and quantities at which the offeror has previously sold the same or similar items.

Any information submitted must support the price proposed. Include sufficient detail or cross references to clearly establish the relationship of the information provided to the price proposed. Support any information provided by explanations or supporting rational as needed to permit the Contracting Officer and authorized representative to evaluate the documentation.

b) The information submitted shall be at the level of detail described below.

1. Direct Labor

Provide a time-phased (e.g., monthly, quarterly, etc.) breakdown of labor hours, rates, and cost by appropriate category. Key personnel will be separately estimated as above and identified. Give the basis for the estimates in each case.

2. Materials

Provide a consolidated price summary of individual material quantities included in the various tasks, orders, or contract line items being proposed and the basis for pricing (vendor quotes, invoice prices, etc.).

3. **Subcontracted Items**

Include parts, components, assemblies, and services that are to be produced or performed by others in accordance with offeror's design, specifications, or direction and that are applicable only to the prime contract. For each subcontract over $650,000, the support should provide a listing by source, item, quantity, price, type of subcontract, degree of competition, and basis for establishing source and reasonableness of price, as well as the results of review and evaluation of subcontract proposals when required by FAR 15.404-3.

4. **Raw Materials**

Consists of material in a form or state that requires further processing. Provide priced quantities of items required for the proposal.

5. **Purchased Parts**

Includes material items not covered above. Provide priced quantities of items required for the proposal.

6. **Fringe Benefits**

Show fringe benefits as a separate line item. Include the rate(s) and/or method of calculating fringe benefits. Provide a copy of your fringe benefit rate or institutional guidelines.

7. **Indirect Costs**

Indicate how offeror has computed and applied offeror's indirect costs, including cost breakdowns, and provide a basis for evaluating the reasonableness of proposed rates. Indicate the rates used and provide an appropriate explanation. Where a rate agreement exists, provide a copy.

8. **Special Equipment**

If direct charge, list any equipment proposed including description, price, quantity, total price, purchase or lease, and the basis for pricing.

9. **Travel**

Provide the cost of travel including destination, duration, purpose, per diem, transportation, and the basis for pricing.

10. **Other Costs**

List all other costs not otherwise included in the categories described above (e.g., computer services, consultant services) and provide basis for pricing.

(4) **Requirements for Cost or Pricing Data or Information Other than Cost and Pricing Data** [FAR Clause 52.215-20 (October 1997)]

(a) Exceptions from cost or pricing data.

(1) In lieu of submitting cost or pricing data, offerors may submit a written request for exception by submitting the information described in the following subparagraphs. The Contracting Officer may require additional supporting information, but only to the extent necessary to determine whether an exception should be granted, and whether the price is fair and reasonable.

(i) Identification of the law or regulation establishing the price offered. If the price is

controlled under law by periodic rulings, reviews, or similar actions of a governmental body, attach a copy of the controlling document, unless it was previously submitted to the contracting office.

(ii) Commercial item exception. For a commercial item exception, the offeror shall submit, at a minimum, information on prices at which the same item or similar items have previously been sold in the commercial market that is adequate for evaluating the reasonableness of the price for this acquisition. Such information may include--

(A) For catalog items, a copy of or identification of the catalog and its date, or the appropriate pages for the offered items, or a statement that the catalog is on file in the buying office to which the proposal is being submitted. Provide a copy or describe current discount policies and price lists (published or unpublished), e.g., wholesale, original equipment manufacturer, or reseller. Also explain the basis of each offered price and its relationship to the established catalog price, including how the proposed price relates to the price of recent sales in quantities similar to the proposed quantities;

(B) For market-priced items, the source and date or period of the market quotation or other basis for market price, the base amount, and applicable discounts. In addition, describe the nature of the market;

(C) For items included on an active Federal Supply Service Multiple Award Schedule contract, proof that an exception has been granted for the schedule item.

(2) The offeror grants the Contracting Officer or an authorized representative the right to examine, at any time before award, books, records, documents, or other directly pertinent records to verify any request for an exception under this provision, and the reasonableness of price. For items priced using catalog or market prices, or law or regulation, access does not extend to cost or profit information or other data relevant solely to the offeror's determination of the prices to be offered in the catalog or marketplace.

(b) Requirements for cost or pricing data. If the offeror is not granted an exception from the requirement to submit cost or pricing data, the following applies:

(1) The offeror shall prepare and submit cost or pricing data and supporting attachments in accordance with Table 15-2 of FAR 15.408.

(2) As soon as practicable after agreement on price, but before contract award (except for unpriced actions such as letter contracts), the offeror shall submit a Certificate of Current Cost or Pricing Data, as prescribed by FAR 15.406-2.

(End of provision)

Alternate I (October 1997). As prescribed in 15.408(l), substitute the following paragraph (b)(1) for paragraph (b)(1) of the basic provision:

(b)(1) The offeror shall submit cost or pricing data and supporting attachments in the following format:

The format specified in paragraph L.2.c.(4) Cost and Pricing Data, subparagraph 3. Formats for Submission of Line Item Summaries shall be used for the submission cost information. Submission of all other cost or pricing data shall be in accordance with Table 15-2 in FAR 15.408.

Alternate I (October 1997) of FAR Clause **52.215-20**, **Requirements for Cost or Pricing Data or Information Other than Cost and Pricing Data** (October 1997). As prescribed in 15.408(l), **substitute the following paragraph (b)(1) for paragraph (b)(1) of the basic provision:**

(b)(1) The offeror shall submit cost or pricing data and supporting attachments in the following format:

The format specified in paragraph L.2.c.(4), Cost and Pricing Data, subparagraph 3. Formats for

Submission of Line Item Summaries shall be used for the submission cost information. Submission of all other cost or pricing data shall be in accordance with Table 15-2 in FAR 15.408.

(5) **Salary Rate Limitation in Fiscal Year 2007**

Offerors are advised that pursuant to P.L. 110-005**, no NIH Fiscal Year 2007 (October 1, 2006 - September 30, 2007) funds may be used to pay the direct annual salary of an individual through any contract awarded as a result of this solicitation at a rate in excess of the Executive Schedule, Level I* (direct salary is exclusive of Overhead, Fringe Benefits and General and Administrative expenses, also referred to as "indirect cost" or "facilities and administrative (F&A) costs"). Direct salary has the same meaning as the term "institutional base salary." An individual's direct salary (or institutional base salary) is the annual compensation that the contractor pays for an individual's appointment whether that individual's time is spent on research, teaching, patient care or other activities. Direct salary (or institutional base salary) excludes any income that an individual may be permitted to earn outside of duties to the contractor.

This does not preclude the offeror from absorbing that portion of an employee's annual salary (plus the dollar amount for fringe benefits and associated indirect costs) that exceeds a rate of the Executive Schedule, Level I*. The salary rate limitation set by P.L. 110-005** applies only to Fiscal Year 2007 funds, however, salary rate ceilings for subsequent years may be included in future DHHS appropriation acts. Multi-year contracts awarded pursuant to this solicitation may be subject to unilateral modifications by the Government if an individual's annual salary exceeds any salary rate ceiling established in future appropriations acts. The Executive Schedule, Level I* annual salary rate limitation also applies to individuals proposed under subcontracts; however, it does not apply to consultants. P.L. 110-005** states in pertinent part:

> "None of the funds appropriated in this Act for the National Institutes of Health, the Agency for Healthcare Research and Quality, and the Substance Abuse, and Mental Health Services Administration shall be used to pay the salary of an individual through a grant or other extramural mechanism at a rate in excess of Executive Level I*."

LINK TO FY 07 EXECUTIVE SCHEDULE SALARIES: http://www.opm.gov/oca/07tables/html/ex.asp

***Note to Offerors:** The current Fiscal Year Executive Level I Salary Rate should be adhered to in the preparation of your proposal. All costs associated with any resultant contract award shall be in compliance with the current Fiscal Year 2007 Executive Level I Salary rates.*

***Public Law 110-005, Revised Continuing Appropriations Resolution, 2007, extends the legislative provisions provided in the FY 2006 Appropriations Act (Public Law 109-149) through the end of FY 2007. Therefore, the provision that restricts the amount of direct salary to Executive Level I of the Federal Executive Pay Scale continues through FY 2007. The Executive Level I annual salary rate was $183,500 for the period January 1 through December 31, 2006. Effective January 1, 2007, the Executive Level I salary rate increased to $186,600.*

(6) **Small Business Subcontracting Plan**

If the proposed contract exceeds a total estimated cost of $550,000 for the entire period of performance, the offeror shall be required to submit an acceptable subcontracting plan in accordance with the terms of the clause entitled "Small Business Subcontracting Plan," FAR Clause No. 52.219-9, incorporated herein by reference in the Solicitation, See SECTION J - LIST OF ATTACHMENTS, BUSINESS PROPOSAL ATTACHMENTS of this RFP for an example of such a plan.

a) THIS PROVISION DOES NOT APPLY TO SMALL BUSINESS CONCERNS.

b) The term "subcontract" means any agreement (other than one involving an employer-employee relationship) entered into by a Federal Government prime contractor or subcontractor calling for supplies or services required for the performance of the original contract or subcontract. This includes, but is not limited to, agreements/purchase orders for supplies and services such as

equipment purchase, copying services, and travel services.

c) The offeror understands that:

(1) No contract will be awarded unless and until an acceptable plan is negotiated with the Contracting Officer which plan will be incorporated into the contract, as a material part thereof.

(2) An acceptable plan must, in the determination of the Contracting Officer, provide the maximum practicable opportunity for Small Businesses, Small Disadvantaged Businesses, Women-Owned Small businesses, HUBZone Small Businesses, Veteran-Owned Small Businesses, and Service Disabled Veteran-Owned Small Businesses to participate in the performance of the contract.

(3) If a subcontracting plan acceptable to the Contracting Officer is not negotiated within the time limits prescribed by the contracting activity and such failure arises out of causes within the control and with the fault or negligence of the offeror, the offeror shall be ineligible for an award. The Contracting Officer shall notify the Contractor in writing of the reasons for determining a subcontracting plan unacceptable early enough in the negotiation process to allow the Contractor to modify the plan within the time limits prescribed.

(4) Prior compliance of the offeror with other such subcontracting plans under previous contracts will be considered by the Contracting Officer in determining the responsibility of the offeror for award of the contract.

(5) It is the offeror's responsibility to develop a satisfactory subcontracting plan with respect to Small Business Concerns, Small Disadvantaged Business Concerns, Women-Owned Small Business Concerns, HUBZone Small Business Concerns, Veteran-Owned Small Business Concerns, and Service Disabled Veteran-Owned Small Business Concerns that each such aspect of the offeror's plan will be judged independent of the other.

(6) The offeror will submit, as required by the Contracting Officer, subcontracting reports in accordance with the instructions thereon, and as further directed by the Contracting Officer. Subcontractors will also submit these reports to the Government's Contracting Officer or as otherwise directed, with a copy to the prime Contractor's designated small and disadvantaged business liaison.

d) Each plan must contain the following:

(1) Goals, expressed in terms of percentages of total planned subcontracting dollars, for the use of Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Business Concerns as subcontractors.

(2) A statement of total dollars planned to be subcontracted. A statement of total dollars to be subcontracted to each of the following type of small business concerns: Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses.

(3) A description of the principal types of supplies and services to be subcontracted with an identification of which supplies and services are expected to be subcontracted to Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and/or Service Disabled Veteran-Owned Small Business Concerns.

(4) A description of the method used to develop the subcontracting goals.

(5) A description of the method used to identify potential sources for solicitation purposes.

(6) A statement as to whether or not indirect costs were included in establishing subcontracting goals. If they were, a description of the method used to determine the proportionate share of indirect costs to be incurred with Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses.

(7) The name of the individual employed by the offeror who will administer the offeror's subcontracting program and a description of his/her duties.

(8) A description of the efforts the offeror will make to assure that Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses have an equitable chance to compete for subcontracts.

(9) Assurances that the offeror will include in all subcontracts the contract clause "Utilization of Small Business Concerns." Assure that all subcontractors, other than small businesses, in excess of $550,000 adopt a plan similar to the plan agreed upon by the offeror.

(10) Assurances that the offeror (and any required subcontractors) will cooperate in studies or surveys as required and submit required reports (SF 294 and SF 295) to the Government.

(11) List the types of records the offeror will maintain to demonstrate procedures that have been adopted to comply with the requirement and goals in the plan, including establishing source lists. Also, the offeror shall describe its efforts to locate Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses and award subcontracts to them.

For additional information about each of the above elements required to be contained the subcontracting plan, see FAR Clause 52.219-9, Small Business Subcontracting Plan, and the Sample Subcontracting Plan which is provided as an attachment to this RFP in SECTION J.

HHS expects each procuring activity to establish minimum subcontracting goals for all procurements. The anticipated minimum goals for this RFP are as follows:

23% for Small Business; 5% for Small Disadvantaged Business; 5% for Women-Owned Small Business; 3% for HUBZone Small Business; and 3% for Veteran-Owned Small Business and Service-Disabled Veteran-Owned Small Business.

(7) **HUBZone Small Business Concerns**

Small Business offerors located in underutilized business zones, called "HUBZones," will be evaluated in accordance with FAR Clause 52.219-4, NOTICE OF PRICE EVALUATION PREFERENCE FOR HUBZONE SMALL BUSINESS CONCERNS, which is incorporated by reference in ARTICLE I.3. of this solicitation. Qualified HUBZone firms are identified in the Small Business Administration website at http://www.sba.gov/hubzone.

(8) **Extent of Small Disadvantaged Business Participation**

In accordance with FAR Subpart 15.304(c)(4), the extent of participation of Small Disadvantaged Business (SDB) concerns in performance of the contract in the authorized NAICS Subsectors shall be evaluated in unrestricted competitive acquisitions expected to exceed $550,000 ($1,000,000 for construction) subject to certain limitations (see FAR 19.1202-1 and 19.1202-2(b). The dollar amounts cited above include any option years/option quantities that may be included in this solicitation. The definition of a "small disadvantaged business" is cited in FAR 19.001.

The factor entitled “Extent of Small Disadvantaged Business Participation” as set forth under the Evaluation Criteria in Section M shall be used for evaluation purposes.

The Department of Commerce determines, on an annual basis, by Subsectors, as contained in the North American Industry Classification System (NAICS) code, and region, if any, the authorized SDB procurement mechanisms and applicable factors (percentages). TheNAICS codes can be found at:
http://www.sba.gov/size

The Department of Commerce website for the annual determination for NAICS codes* is:

http://www.arnet.gov/References/sdbadjustments.htm.

**Note: Public Law 103-355 which authorized the SDB Price Evaluation Adjustment (PEA) and associated percentages/factors expired on December 9, 2004, therefore, the percentages shown at this website are no longer applicable.*

Offerors shall include with their offers, SDB targets, expressed as dollars and percentages of total contract value, in each of the applicable, authorized NAICS Subsector(s). The applicable authorized NAICS Subsector(s) for this project is (are) identified elsewhere in this RFP. A total target for SDB participation by the prime contractor, that includes any joint ventures and team members, shall be provided as well as a total target for SDB participation by subcontractors. In addition, offerors must provide information that describes their plans for meeting the targets set forth in their proposal. **This information shall be provided in one clearly marked section of the Business Proposal, which shall describe the extent of participation of SDB concerns in the performance of the contract.**

If the evaluation factor in this solicitation includes an SDB evaluation factor or subfactor that considers the extent to which SDB concerns are specifically identified, the SDB concerns considered in the evaluation shall be listed in any resultant contract. Offerors should note that addressing the extent of small disadvantaged business participation **is not in any way intended to be a substitute** for submission of the subcontracting plan, if it is required by this solicitation. An example of the type of information that might be given (in addition to the narrative describing the plan for meeting the targets) follows:

EXAMPLE

Targets for SDB Participation - NAICS Subsector 223

	SDB Percentage of Total Contract Value	**SDB Dollars**
Total Contract Value- $1,000,000	25%	$250,000
SDB Participation by Prime	10%	$100,000
(Includes joint venture partners and team arrangements)*		
SDB Participation by subcontractors	15%	$150,000

*Note: FAR Subpart 9.6 defines “Contractor team arrangements” to include two or more companies forming a partnership or joint venture to act as a potential prime contractor, or a potential prime contractor who agrees with one or more companies to have them act as its subcontractors on a specific contract or acquisition program. For purposes of evaluation of the SDB participation factor, FAR 19.1202-4 requires that SDB joint ventures and teaming arrangements at the prime level be presented separately from SDB participation by subcontractors.

(9) **Qualifications of the Offeror**

You are requested to submit a summary of your "General Experience, Organizational Experience Related to this RFP, Performance History and Pertinent Contracts."

a) **General Experience**

General experience is defined as general background, experience and qualifications of the offeror. A discussion of proposed facilities which can be devoted to the project may be appropriate.

b) **Organizational Experience Related to the RFP**

Organizational experience is defined as the accomplishment of work, either past or on-going, which is comparable or related to the effort required by this RFP. This includes overall offeror or corporate experience, **but not** the experience and/or past performance of individuals who are proposed as personnel involved with the Statement of Work in this RFP.

c) **Performance History**

Performance history is defined as meeting contract objectives within delivery and cost schedules on efforts, either past or on-going, which is comparable or related to the effort required by this RFP.

d) **Pertinent Contracts**

Pertinent contracts is defined as a listing of each related contract completed within the last three years or currently in process. The listing should include: 1) the contract number; 2) contracting agency; 3) contract dollar value; 4) dates contract began and ended (or ends); 5) description of contract work; 6) explanation of relevance of work to this RFP; 7) actual delivery and cost performance versus delivery and cost agreed to in the contract(s). For award fee contracts, separately state in dollars the base fee and award fee available and the award fee actually received. The same type of organizational experience and past performance data should be submitted.

e) **Pertinent Grants**

List grants supported by the Government that involved similar or related work to that called for in this RFP. Include the grant number, involved agency, names of the grant specialist and the Science Administrator, identification of the work, and when performed.

You are cautioned that omission or an inadequate or inaccurate response to this very important RFP requirement could have a negative effect on the overall selection process. Experience and past performance are factors which are relevant to the ability of the offerors to perform and are considered in the source selection process.

(10) **Other Administrative Data**

a) **Property**

(1) It is DHHS policy that Contractors will provide all equipment and facilities necessary for performance of contracts. Exception may be granted to furnish Government-owned property, or to authorize purchase with contract funds, only when approved by the Contracting Officer. If the offeror is proposing that the Government provide any equipment, other than that specified under Government Furnished Property in the RFP, the proposal must include comprehensive justification which includes:

(a) An explanation that the item is for a special use essential to the direct performance of the contract and the item will be used exclusively for the purpose. Office equipment such as desks, office machines, etc., will not be provided under a contract except under very exceptional circumstances.

(b) No practical or economical alternative exists (e.g., rental, capital investment) that can be used to perform the work.

(2) The offeror shall identify Government-owned property in its possession and/or Contractor titled property acquired from Federal funds, which it proposes to use in the performance of the prospective contract.

(3) The management and control of any Government property shall be in accordance with DHHS Publication (OS) 686 entitled, "Contractor's Guide for Control of Government Property (1990),"

a copy of which will be provided upon request.

c) **Submission of Electronic Funds Transfer Information with Offer, FAR Clause 52.232-38**, (May 1999)

The offeror shall provide, with its offer, the following information that is required to make payment by electronic funds transfer (EFT) under any contract that results from this solicitation. This submission satisfies the requirement to provide EFT information under paragraphs (b)(1) and (j) of the clause at 52.232-34, Payment by Electronic Funds Transfer--Other than Central Contractor Registration.

(1) The solicitation number (or other procurement identification number).
(2) The offeror's name and remittance address, as stated in the offer.
(3) The signature (manual or electronic, as appropriate), title, and telephone number of the offeror's official authorized to provide this information.
(4) The name, address, and 9-digit Routing Transit Number of the offeror's financial agent.
(5) The offeror's account number and the type of account (checking, savings, or lockbox).
(6) If applicable, the Fedwire Transfer System telegraphic abbreviation of the offeror's financial agent.
(7) If applicable, the offeror shall also provide the name, address, telegraphic abbreviation, and 9-digit Routing Transit Number of the correspondent financial institution receiving the wire transfer payment if the offeror's financial agent is not directly on-line to the Fedwire and, therefore, not the receiver of the wire transfer payment.

d) **Financial Capacity**

The offeror shall indicate if it has the necessary financial capacity, working capital, and other resources to perform the contract without assistance from any outside source. If not, indicate the amount required and the anticipated source.

e) **Incremental Funding**

An incrementally funded cost-reimbursement contract is a contract in which the total work effort is to be performed over a multiple year period and funds are allotted, as they become available, to cover discernible phases or increments of performance. The incremental funding technique allows for contracts to be awarded for periods in excess of one year even though the total estimated amount of funds expected to be obligated for the contract are not available at the time of the contract award. If this requirement is specified elsewhere in this RFP, the offeror shall submit a cost proposal for each year. In addition, the following provisions are applicable:

Incremental Funding, HHSAR 352.232-75, (January 2006)

(a) It is the Government's intention to negotiate and award a contract using the incremental funding concepts described in the clause entitled Limitation of Funds as specified in FAR 52.232-22. Under the clause, which will be included in the resultant contract, initial funds will be obligated under the contract to cover the first year of performance. The Government intends to allot additional funds up to and including the full estimated cost of the contract for the remaining years of performance by contract modifications. However, the Government is not obligated to reimburse the Contractor for costs incurred in excess of the periodic allotments, nor is the Contractor obligated to perform in excess of the amount allotted.

(b) The Limitation of Funds clause to be included in the resultant contract, as specified in FAR 52.232-22, shall supersede the Limitation of Cost clause found in the Section I, Contract Clauses.

(End of provision)

f) **Facilities Capital Cost of Money**, FAR 52.215-16, (June 2003)

(This is applicable if you are a commercial organization.)

(a) Facilities capital cost of money will be an allowable cost under the contemplated contract, if the criteria for allowability in FAR 31.205-10(b) are met. One of the allowability criteria requires the prospective Contractor to propose facilities capital cost of money in its offer.

(b) If the prospective Contractor does not propose this cost, the resulting contract will include the clause Waiver of Facilities Capital Cost of Money.

(End of Provision)

If the offeror elects to claim this cost, the offeror shall specifically identify or propose it in the cost proposal for the contract by checking the appropriate box below.

[ ] The prospective Contractor has specifically identified or proposed facilities capital cost of money in its cost proposal and elects to claim this cost as an allowable cost under the contract. Submit Form CASB-CMF (see FAR 31.205-10).

[ ] The prospective Contractor has not specifically identified or proposed facilities capital cost of money in its proposal and elects not to claim it as an allowable cost under the contract.

(11) **Subcontractors**

If subcontractors are proposed, please include a commitment letter from the subcontractor detailing:

a) Willingness to perform as a subcontractor for specific duties (list duties).

b) What priority the work will be given and how it will relate to other work.

c) The amount of time and facilities available to this project.

d) Information on their cognizant field audit offices.

e) How rights to publications and patents are to be handled.

f) A complete cost proposal in the same format as the offeror's cost proposal.

Note: Organizations that plan to enter into a subcontract with an educational concern under a contract awarded under this RFP should refer to the following Web Site for a listing of clauses that are required to be incorporated in Research & Development (R&D) subcontracts with educational institutions:
http://ocm.od.nih.gov/contracts/rfps/FDP/FDPclausecover.htm

(12) **Proposer's Annual Financial Report**

A copy of the organization's most recent annual report must be submitted as part of the business proposal.

(13) **Representations and Certifications - SECTION K**

One copy of SECTION K (which includes FAR Clause 52.204-8 Annual Representations and Certifications) shall be completed and be signed by an official authorized to bind your organization. Additionally, a completed copy of SECTION K shall be submitted from any proposed subcontractor. SECTION K can be found at: http://rcb.cancer.gov/rcb-internet/wkf/sectionk.pdf

(14) **Travel Costs/Travel Policy**

a) **Travel Costs - Commercial**

Costs for lodging, meals, and incidental expenses incurred by Contractor personnel shall be considered to be reasonable and allowable to the extent they do not exceed on a daily basis the per diem rates set forth in the Federal Travel Regulations, General Services Administration (GSA). Therefore, if travel costs are applicable and proposed by offerors, please be advised that they shall be calculated using the per diem rate schedule as established by GSA. Reimbursement of travel costs under any contract awarded from this RFP shall be in accordance with FAR 31.205-46.

b) **Travel Policy**

One copy of the offeror's (and any proposed subcontractor's) written travel policy shall be included in the business proposal (original only). If an offeror (or any proposed subcontractor) does not have a written travel policy, the offeror shall so state.

(15) **Certification of Visas for Non-U.S. Citizens**

Proposed personnel under research projects are not required to be citizens of the United States. However, if non-U.S. citizens are proposed under a contract to be performed in the United States and its outlying areas, then the offeror must indicate in the proposal that these individuals have the required visas.

SECTION M - EVALUATION FACTORS FOR AWARD

(1) **GENERAL**

Selection of an offeror for contract award will be based on an evaluation of proposals against four factors. The factors in order of importance are: technical, cost, past performance and Small Disadvantaged Business (SDB) participation. Although technical factors are of paramount consideration in the award of the contract, past performance, cost/price and SDB participation are also important to the overall contract award decision. All evaluation factors other than cost or price, when combined, are **significantly more important than cost or price**. The Government intends to make an award(s) to that offeror whose proposal provides the best overall value to the Government.

The evaluation will be based on the demonstrated capabilities of the prospective Contractors in relation to the needs of the project as set forth in the RFP. The merits of each proposal will be evaluated carefully. Each proposal must document the feasibility of successful implementation of the requirements of the RFP. Offerors must submit information sufficient to evaluate their proposals based on the detailed criteria listed below.

(2) **EVALUATION OF OPTIONS**

It is anticipated that any contract(s) awarded from this solicitation will contain option provision(s) and period(s).

In accordance with FAR Clause 52.217-5, Evaluation of Options. (July 1990), the Government will evaluate offers for award purposes by adding the total price for all options to the total price for the basic requirement, except when it is determined in accordance with FAR 17.206(b) not to be in the Government's best interests. Evaluation of options will not obligate the Government to exercise the option(s).

(3) **EVALUATION OF DATA SHARING PLAN**

The offeror's plan for the sharing of final research data shall be assessed for appropriateness and adequacy. If your proposal does not include a plan or if the plan in your proposal is considered “unacceptable,” and the Government includes your proposal in the competitive range (for competitive proposals), or if the Government holds discussions with the selected source (for sole source acquisitions), you will be afforded the opportunity to further discuss, clarify or modify your data sharing plan during discussions and in your Final Proposal Revision (FPR). If your data sharing plan is still considered “unacceptable” by the Government after discussions, your proposal may not be considered further for award.

(4) **TECHNICAL EVALUATION CRITERIA**

The evaluation criteria are used by the technical evaluation committee when reviewing the technical proposals. The criteria below are listed in the order of relative importance with weights assigned for evaluation purposes.

OFFERORS AND REVIEWERS ARE ADVISED TO REFER TO - Additional Technical Proposal Instructions – OF THIS SOLICITATION PACKAGE FOR GUIDANCE AND INFORMATION RELATED TO THE PREPARATION OF TECHNICAL PROPOSALS.

CRITERIA **WEIGHT**

CRITERION 1: TECHNICAL PLAN/APPROACH **100**

The offeror's understanding of and ability to carry out the requirements of the Statement of Work as evidenced by the soundness, appropriateness, adequacy and feasibility of the following:

1) Statistical Design, Statistical Analysis, and Case Studies (20)

   a. Statistical Design: Organizational experience and proposed plans and procedures to perform the statistical design and feasibility assessment functions specified in the Statement of Work, including identifying major problems and/or deficiencies encountered in statistical design functions, and recommending and implementing corrective actions.

   b. Statistical Analysis: Organizational experience and proposed plans and procedures to perform the statistical analysis functions for clinical trials and mechanistic/biomarker and assay studies specified in the Statement of Work.

   c. Case Studies: Statistical feasibility assessments of concept proposals and full applications for clinical trials and mechanistic studies:

      i. *Case Study 1*: Concept Proposal Feasibility Assessment – Cytokine Production in Children with Pre-Clinical and Clinical Type 1 Insulin Dependent Diabetes Mellitus
      ii. *Case Study 2*: Concept Proposal Feasibility Assessment – Immune Responses to Natural Rhinovirus Infections in Individuals with Allergic Asthma, Allergic Rhinitis and Controls
      iii. *Case Study 3*: Full Application Feasibility Assessment – Phase II Clinical Trial of Tolerance Induction for Active Rheumatoid Arthritis

2) Development of Clinical Protocols, Related Documents, and Regulatory Submissions (20)

   a. Protocol Development: Organizational experience and proposed plans and procedures to: (i) assist with the clinical, medical, pharmacological / pharmacokinetic, toxicologic, chemistry and manufacturing aspects of clinical protocol development; and (ii) identify common problems and difficulties encountered in developing clinical protocols, and recommend and implement corrective actions.

   b. Protocol-Related Documents and Materials: Organizational experience and proposed plans and procedures for preparing and/or assisting in the preparation of protocol-related documents required for the implementation of clinical trials.

   c. Regulatory Submissions: Organizational experience and proposed plans and procedures to assist with preparing statistical design and analysis components, documents, and materials for pre- and post-IND submissions, annual INDreporting, and written communications and oral presentations to regulatory health authorities.

3) Data Management, Safety Oversight and Reporting (20)

   a. Database I and II and Data Quality Control: The proposed computer-based systems and plans and procedures for system implementation, operation, maintenance, and data quality control for Database I (clinical and laboratory data, and Adverse Events), and for Database II (Serious Adverse Events).

   b. Safety Oversight and Reporting: Organizational experience and proposed plans and procedures for carrying out the safety oversight and reporting functions specified in the Statement of Work.

4) Study Communications, Internet-based Collaboration Portals, and Clinical Site Training (20)

   a. Study Communication, Collaboration and Reporting: Organizational experience and proposed plans and procedures for coordinating SDCC functions and activities in collaboration with other DAIT clinical

research support services contractors.

b. Clinical Study Internet-based Collaboration Portals: Organizational experience and proposed plans and procedures to establish, maintain, and update clinical study collaboration portals.

c. Clinical Site Training, Assessment and Technical Assistance: Organizational experience and proposed plans and procedures for developing and conducting training for clinical site personnel, conducting site assessments of data entry and management systems of ITN-supported study sites, and collaborating with the DAIT Clinical Site Monitoring Group to plan and conduct site initiation visits.

5) Initial Transition (20)

Proposed plan for the secure, orderly and efficient transfer and/or receipt of clinical and laboratory data, study-related materials, and other contract-generated resources, including (i) timelines and detailed plans to ensure a seamless transition of currently enrolling studies; (ii) detailed plans for database transition; and (ii) plan to provide final study reports and other required regulatory reports for all studies in transition.

CRITERION 2: SCIENTIFIC AND TECHNICAL PERSONNEL **25**

1) Principal Investigator: Appropriateness and adequacy of the education, training, experience, expertise and effort of the proposed Principal Investigator with respect to the statistical design, development and analysis of all phases of clinical trials; management, coordination and oversight of statistical design and analysis components of pre-IND and IND submissions; design and management of data collection and quality control systems; management and coordination of safety oversight and reporting functions; the provision of statistical design and data coordination functions in support of clinical trial networks and other regulatory, monitoring and support service organizations; and interactions and collaborations with government sponsors, government-supported clinical investigators and clinical trial networks, and industry collaborators in protocol design, development, execution, oversight, analysis and reporting.

2) Other Scientific and Technical Personnel: Appropriateness and adequacy of the education, training, experience, expertise and effort of other proposed scientific and technical personnel of the offeror and all proposed subcontractors, including the adequacy of the proposed mix of staff, expertise, experience, and training, to carry out contract requirements with respect to the following:

a. statistical design and analysis;
b. specialized services for the development of clinical protocols;
c. preparation of protocol-related documents and regulatory submissions;
d. preparation and/or evaluation of manufacturing procedures and methods for generating investigational products;
e. safety oversight support, including DSMP development and evaluations of AE and SAE Reports; and
f. information technology support, including database management and website design and maintenance.

CRITERION 3: FACILITIES, EQUIPMENT AND OTHER RESOURCES **20**

The availability and suitability of the facilities, equipment and other resources of the offeror and all proposed subcontractors for conducting the SDCC functions specified in the Statement of Work, including (i) central facilities for data collection, computer processing, storage, tracking and retrieval of study data; (ii) off-site facility for back-up copies of data; (iii) central facility to serve as the Safety Reporting Center and telephone help line; (iv) computers, hardware, software, and security systems in place; (iv) controlled access areas for secure storage of study data and confidential study information; and (v) webcast and video capabilities for training purposes that can be uploaded to the internet

CRITERION 4: PROJECT MANAGEMENT **15**

1) Adequacy of the plan for project management in terms of staffing, organization, responsibilities, leadership and lines of authority, including proposed subcontractors.
2) Suitability of systems proposed for tracking project activities and monitoring progress, timelines, and budgets.

3) Suitability of the plan for how the PI will communicate with the Project Officer and the Contracting Officer, as well as establish, monitor and manage the lines of communication between all performance sites and activities.
4) Suitability of the plan for soliciting, evaluating, negotiating, awarding and managing any proposed subcontracts in accordance with Federal regulations.
5) Adequacy of the experience and education of contract management staff in the acquisition and management of subcontracts under Federal contracts.
6) Adequacy of experience in identifying and remediating subcontractor performance problems or noncompliance with subcontract terms and conditions.

TOTAL POSSIBLE WEIGHT: **160**

EVALUATION OF OPTIONS **20**

No technical evaluation of Option 1 is required as this option is for an extension in time only.

1) Option 2 – Provision of Additional SDCC Support Services for NIAID Asthma and Allergic Diseases Cooperative Research Centers (10)

Ability to expand the scope of SDCC support to include the collection, storage, management, quality control and reporting of data for Phase I and II clinical trials and mechanistic studies conducted by the AADCRC as evidenced by the soundness, appropriateness, adequacy and feasibility of the proposed plans and procedures to provide (i) a computer-based system for data collection, entry, storage and management, including back-up procedures, disaster recovery procedures, and query abilities; (ii) internet-based systems for remote data entry and transmission; (iii) centralized computer-based registration and randomization of subjects; (iv) non-computerized systems for data entry, transmission, registration and randomization, when necessary; (v) systems and procedures for data quality control; (vi) compliance with domestic and non-domestic regulatory requirements; and (vii) sufficient number and type of qualified and experienced staff of the offeror and any proposed subcontractors to carry out the expanded support services.

2) Option 3 – Provision of SDCC Support Services for Additional DAIT Clinical Trial Programs and Projects (10)

Ability to provide SDCC support for additional DAIT clinical trial programs and projects as evidenced by the soundness, appropriateness, adequacy, and feasibility of the proposed plans to: (i) design, conduct, and analysis of additional Phase I-III clinical trials; (ii) expand the existing computer-based systems or establish additional computer-based systems for the collection, storage, management and quality control of study data; (iii) modify or add to the SDCC management structure to accommodate additional oversight responsibilities; and (iv) provide the sufficient number and type of qualified and experienced staff of the offeror and any proposed subcontractors to carry out the expanded support services.

TOTAL POSSIBLE WEIGHT (with Options): **180**

(5) **PAST PERFORMANCE FACTOR**

An evaluation of offerors' past performance information will be conducted prior to any communications with offerors leading to establishment of the competitive range. However, this evaluation will not be conducted on any offeror whose proposal will not be admitted to the competitive range on the basis of the results of the evaluation of factors other than past performance.

(6) **EXTENT OF SMALL DISADVANTAGED BUSINESS PARTICIPATION**

SDB participation will not be scored, but the Government's conclusions about overall commitment and realism of the offeror's SDB Participation targets will be used in determining the relative merits of the offeror's proposal

and in selecting the offeror whose proposal is considered to offer the best value to the Government.

The extent of the offeror's Small Disadvantaged Business Participation Targets will be evaluated before determination of the competitive range. Evaluation of SDB participation will be assessed based on consideration of the information presented in the offeror's proposal. The Government is seeking to determine whether the offeror has demonstrated a commitment to use SDB concerns for the work that it intends to perform.

Offers will be evaluated on the following sub-factors:

(a) Extent to which SDB concerns are specifically identified
(b) Complexity and variety of the work SDB concerns are to perform
(c) Extent of participation of SDB concerns in terms of the value of the total acquisition.

SOLICITATION ATTACHMENTS INCLUDED WITH THE RFP

The following pages include Attachments applicable to this RFP as specified in SECTION J - List of Attachments

PACKAGING AND DELIVERY OF THE PROPOSAL

PAPER SUBMISSION: The paper copy is the official copy for recording timely receipt of proposals.

SUBMISSION OF PROPOSALS BY FACSIMILE OR E-MAIL IS **NOT** ACCEPTABLE.

A. EXTERNAL PACKAGE MARKING:

In addition to the address cited below, mark each package as follows:

"**RFP NO. NIH-NIAID-DAIT-08-10**
TO BE OPENED BY AUTHORIZED GOVERNMENT PERSONNEL ONLY"

B. PAPER COPIES and CD-Rom to:

If Hand Delivery or Express Service	If using U.S. Postal Service
Deborah Blyveis Contract Specialist Office of Acquisitions, DEA, NIAID, NIH 6700-B Rockledge Drive, Room 3214 Bethesda, Maryland 20817	Deborah Blyveis Contract Specialist Office of Acquisitions, DEA, NIAID, NIH 6700-B Rockledge Drive, Room 3214, MSC 7612 Bethesda, Maryland 20892-7612

NOTE: All material sent to this office by Federal Express should be sent to the Hand Carried Address.

NOTE: The U.S. Postal Service's "Express Mail" does not deliver to the hand delivered (20817 zip code) address. Any package sent to this address via this service will be held at a local post office for pick-up. THE GOVERNMENT IS NOT RESPONSIBLE FOR PICKING UP ANY MAIL AT A LOCAL POST OFFICE. If a proposal is not received at the place, date, and time specified herein, it will be considered a "late proposal," in accordance with HHSAR 352.215-70, Late Proposals and Revisions (NOV 1986).

C. NUMBER OF COPIES:

TOTAL PAGE COUNT DOES NOT INCLUDE: Title and Back Page; NIH-2043; Table of Contents; Section Dividers that do not contain information other than title of Section.

PAGES THAT ARE 2-SIDED WILL COUNT AS 2 PAGES.

FORMATTING AND LAYOUT:
Use your usual word processing and spreadsheet programs to prepare and format the technical and business proposals.

Documents submitted using Adobe .pdf shall be submitted using a .pdf searchable format.

- Type size must be 10 to 12 points.
- Type spacing should be no more than 15 characters per inch. Within a vertical inch, there must be no more than six lines of text.
- Print margins must be at least one inch on each edge of the paper.
- Print setup should be single-sided on standard letter size paper (8.5 x 11" in the U.S., A4 in Europe).
- Proposals shall NOT include links to Internet Web site addresses (URLs) or otherwise direct readers to alternate sources of information.

CREATING AND NAMING ELECTRONIC FILES:

1. A separate CD should be submitted for the Technical Proposal and Business Proposal information. *Offerors who submit both Technical and Business Proposals on the same CD will be required to resubmit them on separate CDs.*

2. It is requested that the Technical Proposal be submitted as one document.

   Note: if multiple files are submitted for the either proposal, please include the name of the section in the file name.

   EXAMPLE: XYX Company-08-04-Technical-Approach-3-6-06

3. CDs should be named using the following format:

   Technical Proposal: ***Company name-RFP number-technical-date***
   Business Proposal: ***Company name-RFP number-business-date***

THE NUMBER OF COPIES AND APPLICABLE PAGE LIMITATIONS REQUIRED OF EACH PART OF YOUR PROPOSAL ARE AS SPECIFIED BELOW.

PAGES IN EXCESS OF THIS LIMITATION WILL BE REMOVED FROM THE PROPOSAL AND WILL NOT BE PROVIDED TO THE REVIEWERS TO BE READ OR EVALUATED.

OFFERORS MUST CERTIFY THAT THE INFORMATION IN THE PAPER AND ELECTRONIC COPIES IS EXACTLY THE SAME.

Document	Number of Copies	Page Limits
Technical Proposal and all Appendices	**PAPER** One (1) unbound SIGNED ORIGINAL. Six (6) unbound COPIES **ELECTRONIC FILES ON CD** Three (3) Compact Disks containing an electronic copy of the Technical Proposal (including all Appendices)	**Not to Exceed 300 pages (inclusive of all Attachments and Appendices)**
Business Proposal	**PAPER** One (1) unbound SIGNED ORIGINAL. Five (5) unbound COPIES **ELECTRONIC FILES ON CD** Three (3) Compact Disks containing an electronic copy of the Business Proposal	N/A
Breakdown of Proposed Estimated Cost using Electronic Cost Proposal EXCEL Workbook	This Attachment to the Business Proposal should be submitted as a separate EXCEL file on the Business Proposal Compact Disk. **See Section J, Attachment entitled Breakdown of Proposed Estimated Costs (plus Fee) with Excel Spreadsheet to access the Excel Workbook.**	N/A

ATTACHMENT 2: STATEMENT OF WORK

STATISTICAL AND DATA COORDINATING CENTER (SDCC):
NIAID IMMUNE TOLERANCE NETWORK AND
ASTHMA AND ALLERGIC DISEASES COOPERATIVE RESEARCH CENTERS
RFP NIH-NIAID-DAIT-08-10

1) BACKGROUND and INTRODUCTION

Research supported and conducted by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Department of Health and Human Services (DHHS), strives to better understand, treat, and ultimately prevent immunologic, infectious, and allergic diseases. The NIAID Division of Allergy, Immunology, and Transplantation (DAIT) supports extramural basic, pre-clinical and clinical research focusing on immune-mediated diseases, including the development and evaluation of therapeutic, preventive and diagnostic approaches, through a variety of research grants and contracts.

The Immune Tolerance Network (ITN) was established in 1999 and is currently under a contract to the University of California, San Francisco. The ITN involves approximately 70 investigators from more than 40 institutions within the U.S., Canada, Western Europe, the United Kingdom, and Australia. The overall goal of the ITN is to accelerate the evaluation of promising approaches for the induction and maintenance of immune tolerance in four clinical areas: solid organ transplantation, islet cell transplantation, autoimmune diseases, and asthma and allergic diseases. The scope of research carried out by the ITN includes: Phase I, II, III and IV clinical trials conducted at domestic and non-domestic sites; investigations of the mechanisms underlying immune tolerance; studies to identify and evaluate potential immune/surrogate markers of the induction, maintenance, and loss of tolerance in humans; and the operation of several core resources for assays and bioinformatics. Under the contract to be awarded in FY 2007, the ITN will participate in additional research activities, including non-clinical safety and efficacy evaluations and, on a limited basis, manufacture of investigational products.

The NIAID established the Asthma and Allergic Diseases Cooperative Research Centers (AADCRCs) in 1971 to promote integrated, multidisciplinary basic and clinical research on the immunologic mechanisms underlying the onset and progression of asthma and allergic diseases. The overall goal of this program is to improve the diagnosis and treatment of asthma and allergic diseases, and to provide a rational foundation for the development of effective therapeutic and prevention strategies. At present, NIAID supports 15 AADCRCs. Starting in FY 2006 (under Request for Applications (RFA)-AI-05-027: http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-05-027.html), these Centers were required to include a clinical research component. By FY 2008 (under RFA-AI-07-002: http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-05-027.html), all Centers will be conducting clinical research projects, many of which will involve the design, conduct and analysis of Phase I and Phase II clinical trials and mechanistic studies at domestic sites.

Under the current contract to the PPD Corporation (HHSN266200400075C), the SDCC has served to provide a broad range of clinical research support services to the ITN. Under this contract, the Statistical and Data Coordinating Center (SDCC) will support both the ITN and the AADCRCs.

2) SCOPE

The Contractor shall serve as the SDCC for clinical and non-clinical research activities carried out by the ITN with the responsibility for a broad range of support functions, including: statistical design and analysis; clinical data collection, storage, management, quality control, reporting and associated training for clinical site personnel; safety oversight; preparation of study-related materials; and clinical study website development and maintenance. The Contractor shall also serve as the SDCC for the AADCRCs to provide assistance in the statistical design, analysis and final reporting for clinical trials and mechanistic studies.

(Note: Although the ITN generates both clinical and mechanistic data from each trial, the scope of SDCC statistical analysis functions is limited only to clinical data as specified in each protocol. Statistical analysis of mechanistic data and combined data from both clinical trials and mechanistic studies will be performed by the ITN Clinical Trials Group and the ITN Bioinformatics Group).

The contract will be funded for a base period of six (6) years to provide SDCC support for the research activities of the ITN and the AADCRCs. In addition, the Government reserves the right to exercise three (3) options: Option 1 provides for an extension of the contract for one (1) additional year to continue the SDCC support services specified in the base period for both research programs; Option 2 provides for additional SDCC support for data collection, storage, management, quality control and reporting for the AADCRCs; and Option 3 provides SDCC support for other DAIT-sponsored research programs and projects involving clinical research on immune-mediated diseases, including asthma and allergic diseases, solid organ, tissue and cell transplantation, and autoimmune disorders. These other programs and projects that may be supported under Option 3 include new individual clinical trial grants and existing and future clinical research programs/networks and projects awarded by DAIT.

3) TECHNICAL REQUIREMENTS

PART A: IMMUNE TOLERANCE NETWORK STATISTICAL AND DATA COORDINATING CENTER SUPPORT SERVICES

Independently, and not as an agent of the Government, the Contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government, as needed to perform the functions specified below.

In carrying out these functions, SDCC staff shall serve as members of Study Management Teams established for each ITN-approved clinical trial and responsible for working with DAIT staff and ITN-supported investigators in the development of clinical protocols and protocol-related documents, clinical trial execution, safety oversight and reporting, and overall data analysis via the resources provided by the SDCC. In addition, the SDCC Principal Investigator shall serve as a member of the ITN Steering Committee and shall participate in decision-making with regard to Concept Proposals and Full Applications, as well as in the development and implementation of policies, procedures and processes to guide the research activities of the ITN.

1. Statistical Design and Analysis

SDCC support shall be provided to the ITN for: (i) feasibility assessments of Concept Proposals and Full Applications for clinical trials and mechanistic studies proposed for support by the ITN; (ii) statistical design and analysis plans for protocols to conduct ITN-approved Phase I, II, III and IV clinical trials; and (iii) ITN non-clinical studies to assess safety and efficacy in selected animal models of human diseases. Endpoints shall include safety, disease-related assessments of clinical efficacy, determination of dose-ranging minimum effective dose, maximum tolerated dose, optional dose per indication, and dose escalation studies, pharmacokinetics, and pharmacodynamics. Phase III and IV clinical trials conducted by the ITN encompass the evaluation of safety and efficacy, license-enabling studies, and/or post-marketing studies for new indications.

A. Statistical Design

1) *Concept Proposals and Full Applications*: Perform feasibility assessments of Concept Proposals and Full Applications from ITN and non-ITN investigators seeking support for clinical trials. This includes assessing feasibility with respect to the following features of the clinical trials proposed, as well as proposed mechanistic and surrogate/biomarker studies:

   a. study design, analysis plan, and primary and secondary endpoints selected;
   b. number of cohorts and number of participants per cohort;
   c. entry criteria and resulting feasibility of recruitment;
   d. accuracy of statistical power calculations to evaluate the proposed primary safety and efficacy endpoints, including performing simulations of various possible power and sample size calculations using different assumptions and loss-to-follow-up estimates; and
   e. selection of optimal randomization ratios (2:1, 3:1, etc.) between study product/intervention and placebo to optimize the potential for completing enrollment and meeting the stated clinical trial-specific objectives.

2) *Clinical Protocols, Mechanistic and Surrogate/Biomarker Studies*: Develop and refine experimental study designs for ITN-approved clinical trials, including appropriate control/comparison groups, inclusion and exclusion criteria, sample size and power estimates, primary and secondary endpoints, randomization and stratification/blocking methods, and masking approaches. This includes reviewing successive versions of clinical protocols, recommending improvements and modifications in statistical design issues to facilitate recruitment and retention of appropriate study participants, and ensuring the validity of inclusion/exclusion criteria and comparator/control groups. This also includes assessing the validity and reliability of the techniques and methods to be used to delineate underlying mechanisms and to identify and validate surrogate/biomarkers of the induction, maintenance and loss of immune tolerance. In carrying out these support services, a SDCC statistician shall be assigned to each Study Management Team responsible for developing the clinical protocol.

3) *Preclinical Safety Study Evaluations*: Evaluate the statistical accuracy and validity of preclinical safety studies performed in support of ITN clinical trials, including: single and repeated dose acute toxicity studies; local tolerance studies; chronic toxicity studies; pharmacology studies for safety assessment and pharmacokinetic studies (absorption, distribution, metabolism, and execution [ADME]). Such evaluations shall address the accuracy and validity of control/comparison groups, sample size selection, primary and secondary endpoints, randomization and stratification/blocking methods, and masking approaches used for the original and all successive versions of each preclinical safety study protocol.

B. Statistical Analysis

1) *Interim Statistical Analyses:* Perform interim statistical and trend analyses of clinical trial data, including the design and presentation of tables, listings, and graphical figures, for the evaluation of ongoing studies with respect to safety, toxicity, pharmacokinetics, pharmacology, efficacy, and/or exploratory endpoints, as well as surrogate/biomarker studies. Submit Draft Interim Analyses to the Project Officer, other DAIT scientific staff, clinical investigators, and industry collaborators, within 14 calendar days of analysis completion. Revise Draft Interim Analyses in accordance with comments received and submit Final Interim Analyses to the Project Officer, and his/her designees within 14 calendar days of receipt of comments.

2) *Final Statistical Analyses*: Conduct comprehensive final statistical analyses of all clinical trial data, including descriptive as well as univariate and multivariate inferential analyses, in accordance with the approved protocol. Draft Final Statistical Analysis Reports shall be submitted within 30 calendar days of completion of the final data set for review by the Project Officer and others designated by the Project Officer, including other DAIT scientific staff, clinical investigators, members of the ITN leadership and industry collaborators. Revise Draft Statistical Analysis Reports based on comments received, and prepare and submit to the Project Officer Final Statistical Analysis Reports within 30 calendar days of receipt of comments. Attend Study Closeout Meetings for each trial closing.

3) *Electronic Data Transfers*: Prepare and transfer to the ITN Bioinformatics Data Center statistical evaluations of interim and/or final datasets for each ITN clinical trial based on the NIAID Data and Safety Monitoring Board (DSMB) safety review calendar. These electronic data transfers shall be based on and shall include all clinical safety data and limited efficacy data (blinded for blinded clinical trials) as presented to NIAID DSMBs or other NIAID safety oversight structures, and/or ad hoc interim data listings and analyses requested by ITN investigators and approved by the ITN leadership and the Project Officer or his/her designees. These files shall include associated text documents (e.g., cover memoranda) and programmed data files (e.g., tables, listings and figures) per protocol and shall be transferred regularly 2-3 times per month, using software compatible with SAS software (version 8.2 or higher) and transferred in SAS transport (XPORT) files.

4) *Pre-Publication/Presentation Review*: Review the accuracy and completeness of statistical data and data analyses for all abstracts, manuscripts, and presentations reporting on the results studies conducted through the ITN prior to presentation or submission for publication.

2. Protocol Development

The ITN Clinical Trial Group has primary responsibility for protocol development and protocol writing. Within this context, the SDCC shall:

A. Assign a statistician to serve as a member of each Study Management Team (SMT) to provide expert advice and assistance in the development and finalization of statistical designs and statistical analysis plans for clinical protocols.

B. Provide, at the request of the Project Officer, additional specialized support services to assist in the development of protocols for ITN-approved clinical trials. This includes assistance in the preparation of protocol components to address clinical, medical, pharmacological/pharmacokinetic, toxicologic, chemistry and manufacturing aspects of clinical protocols. In carrying out these specialized support services, the SDCC shall independently prepare and/or assist ITN-supported investigators in the preparation of various sections of clinical protocols, review protocol drafts and make recommendations for modifications and improvements in these areas.

3. Protocol-Related Documents and Materials

Independently prepare and/or assist in the preparation of protocol-related documents and materials required for the implementation of clinical trials. This includes:

- Manuals of Operations (MOOs)
- Investigator Brochures (IBs)
- electronic or paper Case Report Forms (CRFs)
- source documents, questionnaires, memory aids and subject instructions
- screening and recruitment logs, order forms for clinical supplies
- test article accountability logs
- Consent forms

4. Regulatory Submissions

Assist the Project Officer, other DAIT scientific staff, ITN-supported clinical investigators and industry collaborators in planning for and conducting the following activities for regulatory submissions for ITN-approved clinical trials:

A. *Investigational New Drug (IND) Applications*: Assist in the preparation of regulatory submissions for INDs to the U.S. Food and Drug Administration (FDA) and to other non-U.S. regulatory authorities with respect to statistical design and analysis issues/plans. This includes assistance in the preparation of pre-IND briefing packets for meetings and teleconferences with regulatory authorities.

B. *Statistical Preparations for Meetings and Teleconferences with Regulatory Authorities*: Assist in preparing written materials and oral presentations on statistical design and analysis issues/plans for meetings and teleconferences with the FDA and other regulatory authorities, and participate in meetings and teleconferences with regulatory authorities to present these aspects of IND clinical trials.

C. *Inquires from Regulatory Authorities*: Assist in responding to inquiries from the FDA and other regulatory authorities regarding clinical trial design and analysis plans both prior to and after study initiation.

D. *Annual Reports to Health Authorities*: Assist in the preparation of statistical and clinical documents required for Annual IND Reports for health authority review for all ITN clinical trials conducted under IND applications, including data tables, listings, and figures to address the following major areas:

1) Individual Study Information (per IND #):
   a. Ongoing Clinical Trials
   b. Completed Clinical Trials

2) Summary Information, including:
   a. Adverse Events by Body System
   b. IND Safety Reports (Serious Adverse Events)
   c. List of Deaths and Causes per trial
   d. List of Dropouts per trial
   e. New Information per trial
   f. Nonclinical Studies per trial

3) Phase I Protocol Modifications (per trial)

E. *Interim Clinical Study Reports*: Prepare an Interim Clinical Study Report at the completion of each ITN clinical trial for review and approval by the Project Officer, his/her designees and the leadership of the ITN. Submit approved Interim Clinical Study Reports to Project Officer and/or his/her designees for submission to the appropriate regulatory health authorities using a standard format compatible with the International Conference on Harmonization (ICH), document E3, Guidance for Industry: Structure and Content of Clinical Study Reports (http://www.pharmacontract.ch/support/su_ich_liste.htm). Interim Clinical Study Reports shall integrate clinical and statistical observations, analyses and conclusions into a single clearly written report that is well organized, free from ambiguity and easy to review. All such reports shall include:

1) clinical and statistical descriptions of the protocol, the target population, and the observed data collected.
2) how the critical design features and endpoints of the study were selected.
3) the observed baseline, treatment, and follow-up data per participant and per group or cohort.
4) clearly labeled tables, listings, and/or figures that identify the important findings and define the subset of participants from which the important findings were generated.

5. Data Management and Reporting

The SDCC shall be responsible for operating and managing state-of-the-art computer-based systems at a central facility and for performing upgrades, validations, and monthly internal audits required to support the servers, back-up servers, databases, software, and network. A Draft Systems Plan for the implementation and maintenance of all computer-based systems shall be submitted for Project Officer approval within 15 calendar days of the effective date of the contract. The Project Officer comments on the Draft Systems Plan shall be provided within 15 calendar days after receipt. The Final Systems Plan, revised as necessary to accommodate Project Officer comments, must be in place within 60 calendar days from the effective date of the contract.

Specifically, the SDCC shall:

A. *Data Collection, Storage and Management (Database I)*: Implement, maintain and manage computer-based system(s) for the collection, storage, management, tracking, and archiving of all clinical and laboratory research data, including adverse events (AE), and for the management and reporting of data and other information for clinical trials and non-clinical studies conducted by the ITN. The system(s) shall have the following features and capacities:

1) Receive, enter, verify, label, process, edit (including within and across form validity, logic, and consistency checks), update, correct, freeze, lock, store, secure, track, retrieve and archive all clinical and clinical laboratory data at a central data management facility.

2) Comply with all current Federal regulations (§21 CFR 11 and/or similar statutes, http://www.fda.gov/cber/guidelines.htm and meet current globally-accepted standards, including International Conference on Harmonization (ICH) E-2, Clinical Safety Data Management, and ICH M-5, Data Elements and Standards for Drug Dictionaries (http://www.ich.org/cache/compo/475-272-1.html and http://www.ich.org/cache/compo/2196-272-1.html, respectively).

3) Central computerized registration and randomization of the majority of subjects on ITN protocols, and non-computerized methods on a limited basis for selected study sites. In addition, a system for off-line data entry for sites with intermittent internet connection shall be provided. Data may be transmitted at a later time when internet connection is available.

4) Computerized study forms and systems for remote data entry and transmission via the internet of subject data from study sites and laboratories to the central data management facility; non-computerized methods when requested by the Program Officer, for example paper Case Report Forms (CRF).

5) Real-time electronic notification of the Project Officer and NIAID Medical Officers designated by the Project Officer, as well as ITN staff, in the event

one or more protocol-specific or NIAID safety review committee-specific data trigger halting rule(s) occur.

6) Compatibility with the systems being used by the DAIT and the ITN (e.g., DAIT Bioinformatics Integration Support and the ITN Bioinformatics Group contractors), and provision of all related software.

7) For Project Officer-designated high priority studies, daily electronic notification to relevant DAIT staff designated by the Project Officer and participating study sites of accrual and study status, including provision of monthly updates to the ITN Bioinformatics Center.

B. *Safety Data Collection and Reporting (Database II)*: Implement, maintain and manage computer-based system(s) to monitor and report Serious Adverse Events (SAEs) for all domestic and non-domestic ITN study sites, including:

1) Establish and maintain one or more databases for the reporting, tracking, and archiving of SAEs.

2) Establish and maintain an internet-based tracking system for the receipt, reporting, and disposition of SAEs for all ITN clinical trials supported under the contract to the Project Officer, other DAIT staff designated by the Project Officer, participating ITN clinical investigators, industry collaborators and independent medical monitor(s) and NIAID safety oversight structures.

3) Ensure that all procedures and systems meet the FDA guidelines and regulations and/or guidelines and regulations required by non-domestic health authorities as related to the processing of SAE reports and safety information. This includes the European Union (EU) Clinical Trial Directive (http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf) regarding the notification of health authorities and other participating investigators in EU member states of suspected serious and unexpected adverse reactions considered to be life-threatening or fatal during the conduct of clinical trials on human subjects in member nations.

4) Ensure that all procedures and systems meet the EU Clinical Trial Directive requirements for the collection, verification, and presentation of serious adverse event/reaction reports, including decoding (unblinding) procedures required for unexpected serious adverse event/reactions in participating member nations (http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf).

C. *Data Quality Control*: Provide for quality control of all clinical and laboratory research data (Database I) and of all SAE data (Database II) collected for clinical trials. Monitor the accuracy, completeness and timeliness of the data submitted from participating study sites. Quality control for clinical trials begins with study initiation/patient enrollment and proceeds to the generation of final data sets. The system shall have the following features and capacities and shall provide for verification of 100 per cent of study data.

1) Computerized validation and error-checking (e.g., range checks, user logics) to evaluate and improve the accuracy, timeliness and completeness of data submitted by study sites.

2) Strategies to assure uniform standardized data collection and appropriate implementation of multi-center studies across participating study sites.

3) Evaluation of data derived from ongoing quality assurance checks generated in connection with clinical trials and inclusion of summaries of quality assurance checks in Quarterly Progress Reports.

4) Perform a manual evaluation of AE verses SAE data entries for query and resolution of the AE (Database I) and SAE (Database II) listings.

5) Investigate new and improved technologies to enhance the efficiency and ease of use of Databases I and II in order to perform automated data comparisons, error checks and quality control, including generation of interim reports that cross-reference SAE data and other data impacting on participant accrual, retention, compliance, loss to follow-up, and other statistical analyses. Provide an assessment and written recommendations to the Project Officer for proposed enhancements and improvements, including a breakdown of the costs associated with implementing enhancements and improvements recommended. Upon written approval from the Project Officer, implement system modifications and improvements within the timeline specified by the Project Officer depending upon the extent of such enhancements and improvements. All plans for any software development must be submitted and approved by the Project Officer and the Contracting Officer prior to implementation.

6) A computerized data query system to notify and request resolution from clinical and laboratory sites when aberrant and/or missing data are identified.

7) Preparation and annual review and revision of manuals and procedures documenting data collection, editing and validation procedures and standards.

D. *System Security*: Provide for security against anticipated risks, including loss of confidentiality of subject electronic records and data summaries, and catastrophic loss of study data or important software, including an off-site secured storage facility for system back-ups.

1) References for system security information and guidance are located in Section H of the contract at the end of the Article entitled "Information Security."

2) A System Security Plan (SSP) that identifies and details the management, operation, and technical controls of the system. The SSP shall also minimally include the Risk Analysis (RA) and the Continuity of Operations Plan (COOP -- also known as the Contingency Plan). Detailed guidance information regarding the SSP may be found at the following link: http://irm.cit.nih.gov/nihsecurity/NIH_System_C&A.htm. In addition, the contract shall certify that appropriate background checks, equivalent to

federal requirements, have been performed with respect to the informatics employees (such as data managers, analysts, LAN people, etc) who will handle sensitive data including, but not limited to clinical trial patient data, financial data and who would administer use of government furnished equipment. This is to be done before the award. The Contractor may also be required to perform more extensive security checks on personnel handling sensitive data as requested by the Project Officer or Contracting Officer either before award or during the contract period of performance.

3) The preparation and submission of an annual Information System Security Plan (ISSP), following the instructions in the HHS SecureOne Policy http://www.hhs.gov/ocio/policy/index.html#Security, for review and approval by the Project Officer and the NIAID Information System Security Officer (ISSO).

4) A log or record of the results from testing the COOP, any existing plans and progress reports for implementing additional security safeguards and controls, and the system access authorization list. The profile shall be kept up-to-date for review and potential inspection upon demand by NIH/DHHS authorized agents. Upon request, copies of specified profile documents shall be presented to NIH/DHHS for its own system's security reporting requirements.

5) The preparation and submission, for Project Officer approval, of a RA following the guidance given in the HHS SecureOne Policy. The RA is to be maintained and updated every three years, or in advance of implementing major system modifications or enhancements.

6) The development and maintenance of an up-to-date COOP following the guidance in the HHS SecureOne Policy. At a minimum, the COOP shall cover emergency operations, backup operations, and recovery plans to assure continuous operations of the system's facility. COOP testing shall be conducted and the results recorded at least every six months.

7) Plans, procedures and a recommended schedule and budget for implementation of security safeguards required to satisfy the anticipated conditions of acquiring data from the clinical and laboratory sites. This includes data integrity and security during electronic transmission or during transit from the study sites to the Contractor if non-electronic data transmission is used. All subject identifiable data are subject to the Privacy Act, Health Insurance Portability and Accountability Act (HIPAA) and DHHS regulations.

6. Safety Oversight and Reporting

In carrying out the safety oversight and reporting functions specified below, the SDCC shall serve as a member of Study Management Teams (SMT) established for each ITN-approved clinical trial and responsible for working with NIAID staff, ITN-supported investigators and industry collaborators in the development of clinical protocols and protocol-related documents, clinical trial execution, and overall clinical data analysis via the resources provided by the SDCC. This includes working with NIAID Medical Officers assigned to each SMT to serve as "Medical Monitors" for ITN

clinical trials to assist in carrying out medical safety oversight functions to ensure the overall safety and well-being of all study participants.

As part of their duties, SMTs also develop formal Data and Safety Monitoring Plans to ensure appropriate monitoring of the safety of all human subjects participating in ITN-supported clinical trials, and are responsible for ensuring appropriate implementation of safety procedures and adherence to safety oversight and reporting requirements.

A. *Data and Safety Monitoring Plans*: Assist in the development of Data and Safety Monitoring Plans (DSMPs) to ensure appropriate monitoring of the safety of study participants in ITN-sponsored clinical trials in accordance with all applicable Federal and International Conference on Harmonization (ICH) (http://www.pharmacontract.ch/support/su_ich_liste.htm) standards for human subjects research.

B. *NIAID Safety Oversight Structures*: Assist in carrying out a variety of functions associated with ensuring the safety of clinical trial study participants through safety monitoring by NIAID-established oversight structures, including Data and Safety Monitoring Boards (DSMBs), Safety Management Committees (SMCs), and Independent Safety Monitors (ISMs) as commensurate with the anticipated level of risk. All analyses, oral presentations, written responses to questions and documentation of recommendations from safety oversight structures shall be reviewed by the NIAID Medical Monitor and revised, as necessary, based on the NIAID Medical Monitor comments. In addition, such documents and materials shall undergo review, at the discretion of the Project Officer, by other DAIT scientific staff, ITN-supported clinical investigators and industry collaborations. The safety oversight functions to be performed include the following:

1) *Final Draft and All Subsequent Protocol Amendment Reviews*: Arrange for the distribution of Final Draft Protocols and all subsequent protocol amendments for ITN-supported clinical trials to members of NIAID safety oversight structures for review and comment, particularly with respect to protocol-specific DSMPs; review recommendations in conjunction with the Project Officer and his/her designees to determine appropriateness/acceptability; and modify Final Draft Protocols as necessary to implement recommendations of safety oversight structures.

2) *DSMB Review for Ongoing Clinical Trials*: During the course of ongoing clinical trials and at the request of the Project Officer, assist in arranging for DSMPs to be reviewed periodically by NIAID safety oversight structures and in modifying DSMPs in accordance with Project Officer-approved recommendations of NIAID safety oversight structures.

3) *Interim Analyses*: In accordance with the requirements set forth in protocol-specific DSMPs and more frequently, if necessary, at the request of the Project Officer: (i) prepare and distribute separate interim analyses of blinded and unblinded study data, including narrative summaries, tables, listings and graphs/figures, for review at both open and closed sessions of meetings and teleconferences of NIAID safety oversight structures; (ii) prepare and distribute transmittal memoranda highlighting interval changes in safety, efficacy, or other parameters relevant to safety

oversight by such structures; and (iii) prepare and make oral presentations at meetings and teleconferences of NIAID safety oversight structures to explain the results of interim analyses and address questions on patient safety. All such interim analyses and oral presentations shall be submitted for Project Officer review and approval no later than 21 calendar days prior to scheduled meetings/teleconferences of NIAID safety oversight structures and shall be modified, as necessary, to accommodate Project Officer comments. Final materials for meetings and teleconferences of NIAID safety oversight structures shall be submitted to the Project Officer no later than 14 calendar days prior to scheduled meetings and teleconferences.

4) *Documentation of Recommendations of NIAID Safety Oversight Structures*: Prepare written summaries, in accordance with NIAID DSMB Policy, of the deliberations and recommendations of NIAID safety oversight structures. In most instances, all written summaries shall be prepared for review by the Project Officer and his/her designees within 7 calendar days of meeting/teleconference completion and revised in accordance with comments received. Final summaries shall be prepared and submitted to the Project Officer and his/her designees within 5 calendar days of receipt of comments.

   In instances where NIAID accepts the recommendation of a safety oversight structure to change an ongoing study (e.g., stop a trial or discontinue one arm of a trial), written summaries documenting the recommendation shall be prepared within 2 calendar days of completion of meeting/teleconference. In such instances, the SDCC shall also assist in preparing and coordinating communications with NIAID staff, clinical investigators and other study site personnel.

5) *Responses to Recommendations of NIAID Safety Oversight Structures*: Prepare written responses to recommendations resulting from review of data by NIAID Safety Oversight Structures in collaboration with the Project Officer and his/her designees.

C. *Safety Reporting*: Establish and operate a Safety Reporting Center for all ITN-supported clinical trials to carry out safety oversight functions and ensure compliance with all applicable regulatory requirements and principles of Good Clinical Practice (GCP) governing research involving human subjects. This includes the following activities:

1) Establish, operate and maintain an internet data entry system for collecting Adverse Event (AE) and Serious Adverse Event (SAE) Reports from study sites participating in ITN clinical trials. Develop and distribute standard operating procedures for AE and SAE reporting by study site personnel and provide training in the use of the internet data entry system. Paper case report forms for the submission of AE and SAE Reports shall be used strictly as a "back-up system" for the main paperless remote data entry and capture systems for all AEs and SAEs.

2) Prepare and distribute to participating study sites protocol-specific AE and SAE reporting forms, developed in accordance with the requirements and anticipated level of risk as defined in the Final Protocol, and protocol-

specific instructions detailing events to be documented, clinical data to be recorded, grading and attribution. All such AE and SAE reporting forms shall conform to guidelines and regulations of the FDA and/or other regulatory authorities, and shall be developed in coordination with members of the Study Management Team. Forms and instructions shall be submitted to the Project Officer no later than 15 calendar days after completion of the Final Protocol, revised if necessary in accordance with Project Officer comments, and must be approved prior to randomization of study participants.

3) Establish, staff and operate a telephone help line to respond to inquiries about clinical events from study site personnel and to obtain AE and SAE Report information during the hours of 8 a.m. to 6 p.m. Eastern Standard Time, Monday through Friday. Ensure that appropriately trained staff is available to respond to inquiries and obtain information. Provide an automated message service after working hours, on weekends, and on all holidays to record inquiries, and maintain one trained person to be on-call after working hours, on weekends, and on all holidays to respond to inquiries.

4) Within 24 hours of receipt, evaluate all SAE Reports submitted, including SAE narrative and initial/follow-up data submitted by the investigator, investigator's assessment of severity, and the medical management plan employed for the event; request additional information, if necessary, from clinical investigators to complete the SAE Report; and abstract a summary of the SAE narrative and enter the abstract into the safety database for the clinical trial.

5) Establish and implement a system for the immediate notification of all SAEs to the members of the appropriate Study Management Team. The IND sponsor shall be responsible for disseminating SAE Reports to health authorities, all clinical investigators, and the industry collaborators.

6) Prepare and electronically distribute to the DAIT Regulatory Management Center SAE Safety Reports or Information Reports as defined in the established FDA, NIH, NIAID, or pertinent non-domestic health authority guidelines and regulations.

7) At the request of the Project Officer, prepare and submit reports documenting study site performance with respect to safety reporting as measured by the accuracy, completeness and timeliness of AE and SAE Reports, time required for response to queries, monthly missing case report forms per trial and per site, and site screening logs per trial and per site.

7. Clinical Study Internet-based Collaboration Portal

A. Establish, maintain and update, on an ongoing basis, one or more internet-based collaboration portals to house clinical trial information and study-specific documents and materials. Protocol-specific, password-protected websites shall contain the following study-specific information and documents and shall provide access for the Project Officer, other DAIT staff, ITN clinical investigators and other study site personnel and industry collaborators.

1) draft and final protocols and protocol amendments;
2) consent forms;
3) Investigator Brochures and/or package inserts;
4) MOOs containing instructions for clinical site staff regarding study procedures;
5) Case Report Forms for the collection of required data on study subjects, including eligibility, demographics (including age, gender and ethnicity), sequential clinical and laboratory outcome assessments, and acute and long-term adverse events;
6) source documents;
7) instructions for study participants;
8) tracking and dispensing logs;
9) order forms for test articles and clinical supplies;
10) logs of frequently asked questions with answers;
11) other materials at the discretion of the Project Officer and/or relevant DAIT staff; and
12) real-time standard and study-specific data by site and total overall, including accrual, adverse event and serious adverse event listings, protocol deviations, missing forms, visit schedule compliance, data queries, and progress monitoring information/materials.

B. Update all website documents and materials, including new or modified versions of study-specific documents, during the course of all clinical trials, and provide e-mail notifications of the availability of new or revised documents and materials to all individuals with authorized website access.

C. Within 30 calendar days of the effective date of the contract, submit for Project Officer review, a draft plan for the design, establishment, maintenance and updating of collaboration portal(s). Revise the draft plan in accordance with Project Officer comments, and submit the final plan within 10 calendar days of receipt of Project Officer comments.

D. Implement the approved plan and ensure that collaboration portals for all ongoing and planned clinical trials are fully operational within 60 days of the effective date of the contract.

8. Study Communication, Collaboration, and Reporting

Coordinate and collaborate with the Project Officer, other DAIT staff, other DAIT-supported clinical research support services contractors, and the ITN Bioinformatics Center to facilitate study implementation, assess study progress, and evaluate processes and procedures in the following areas:

A. *DAIT Regulatory Management Center*:
1) Download from the DAIT Regulatory Management Center, review, and reconcile with site-specific laboratory normal reference ranges for clinical laboratories from each ITN participating study site for each clinical trial.

2) Plan and develop materials for study initiation meetings to provide training for clinical site personnel with respect to standard and protocol-specific procedures for the collection, entry and submission of clinical trial data to the SDCC central data management facility, standard and study-specific

procedures and instructions for the preparation and submission of AE and SAE Reports to the Safety Reporting Center; and access to and use of Collaboration Portals; participate in study initiation meetings to provide appropriate training for study site personnel.

3) Assist in planning and develop materials for meetings and teleconferences with the FDA and other regulatory authorities; prepare specific statistical components for IND applications and Annual IND Reports to the FDA and other regulatory authorities.

B. *DAIT Clinical Site Monitoring Group*:

1) Plan for and participate in specific aspects of site monitoring visits and, where appropriate, identify and verify deficiencies and recommend remedial actions to address deficiencies identified during data submission (e.g., numerous protocol deviations, incomplete or missing CRFs, etc.) or during previous site visits (e.g., selection of computerized data elements to be verified).

2) Provide data entry screens and/or data listings for the DAIT Clinical Site Monitoring Group, or other NIAID contractors providing safety monitoring functions as needed, to document and record site monitoring reviews and to provide a status update of monitoring progress for each study at each participating study site.

C. *DAIT Drug Distribution Center*:
Assess compliance with randomization and appropriate administration of test articles and study products with documentation of the quantity of test article shipped to each study site and the quantity of test article in stock, as verified by the clinical site monitor.

D. *DAIT Bioinformatics Integration Support (BISC) Contractor and ITN Bioinformatics Group*:

1) Provide periodic data transfers (using SAS data transport files) from the SDCC to the BISC contractor and to the ITN Bioinformatics Group at regular intervals during the conduct of each study based on the NIAID DSMB event calendar, at the completion of interim study reports, and at the completion of the final study reports.

2) Provide periodic input and one formal written review of final draft study reports for each clinical trial prepared by the ITN Bioinformatics Group according to the "ICH E3 Guidelines for Industry: Structure and Content of Clinical Study Reports," including an analysis of both clinical and mechanistic data observed during the trial.

9. Clinical Site Training, Assessment, and Technical Assistance

A. *Clinical Site Training*: Participate in planning and conducting training for clinical site personnel, including clinical investigators, study coordinators, research nurses, data managers and data entry staff. Training topics shall include: (i) procedures for study implementation in accordance with approved protocols, including MOOs, CRFs, and study participant instructions; (ii) design of data collection instruments/materials; (iii) instructions for the collection, entry, management, validation and quality control of study data,

audit trails, and transfer of study data to the central data management facility; and (iv) use of internet data entry system and telephone help line for safety reporting. Such training shall be conducted via meetings, teleconferences, webcasts and videocasts, as determined by the Project Officer, including face-to-face training at clinical sites or at investigator group meetings. All such training activities shall be coordinated with the appropriate DAIT clinical research support services contractors as specified in item 8 above. Specifically, the SDCC shall:

1) Within 60 calendar days of the effective date of the contract, prepare and make available to the Project Officer, other DAIT staff and ITN study and laboratory sites a user's manual for the SDCC internet data entry system.

2) Within 60 calendar days of the effective date of the contract, design and implement a "training data entry module" on the use of the internet data entry system to allow clinical and laboratory site staff to learn, practice and refresh skills in the use of the data entry system.

3) Prepare instructional materials regarding study-specific procedures and conduct training for study site staff, including clinical investigators, study coordinators, research nurses, where applicable, data managers and data entry personnel.

4) Provide consultation and assistance to all participating study sites in establishing or modifying the SDCC internet data entry system and in establishing quality assurance procedures.

B. *Clinical Site Assessment and Technical Assistance*:

1) Assess the capabilities of ITN-supported study sites that are not able to utilize SDCC internet data entry and management systems to collect, enter, secure, validate, manage and submit clinical trial data, including on-site technical expertise and data systems in place for these functions. Provide a written report of the findings of such assessments to the study sites, the Project Officer and other DAIT staff designated by the Project Officer within 30 calendar days of completion of assessments; provide guidance, direction and follow-up to assist such sites in establishing and maintaining data systems in accordance with ICH and GCP guidelines, http://www.ich.org/cache/compo/276-254-1.html.

2) In collaboration with the DAIT Clinical Site Monitoring contractor, assist in planning for and participate in site initiation visits, when necessary, to assess the capabilities of study sites to conduct clinical trials in accordance with all regulatory requirements and guidelines governing research involving human subjects. SDCC participation in site initiation visits shall encompass assessments of computer equipment, facilities and systems, plans and procedures for data quality control and safety reporting, and designated site personnel assigned to carry out these functions.

10. Facilities, Equipment and Other Resources

The Government will not provide any government-furnished equipment nor funds from this contract to purchase government-furnished equipment. The offeror will

provide and maintain the following facilities, equipment and other resources to carry out the requirements set forth in the Statement of Work for the entire contract period of performance:

A. A central facility for the collection, computer processing, storage, tracking and retrieval of all study data and study-related information.

B. All computer equipment, hardware and software, and servers.

C. Resources to ensure secure internet access.

D. Controlled access areas for secure storage of study data and confidential study information.

E. An off-site, separate, secure and access-controlled facility for back-up copies of data.

F. Web-cast and video-cast capability for training purposes that can be uploaded to the internet.

11. Initial and Final Transitions

A. Initial Transition:

1) In the event of a new contractor, coordinate with the incumbent contractor to implement an orderly, secure and efficient initial transition of contract-generated data and other documents and materials. A copy of the transition plan of the incumbent contractor will be provided and will include detailed instructions on the data management and quality control system(s), as well as specific study records and datasets, including studies open for enrollment, in follow-up, closed, and in analysis. Contract-generated data and materials to be transitioned include the following:

a. draft protocols for clinical trials in development, final protocols and protocol amendments for ongoing clinical trials, and final protocols and protocol amendments for completed clinical trials;
b. all study-related materials for ongoing and completed clinical trials, as well as clinical trials in development, including CRFs, MOOs, IBs, etc.;
c. data and other information contained in study-specific websites and procedures for access control;
d. all materials prepared for meetings, teleconferences and responses to inquiries from the FDA and other regulatory authorities;
e. users manuals and all written instructions for utilization of the SDCC data management system; and
f. instructions and standard operating procedures for safety reporting.

The Contractor must be prepared to receive all data and study-related documents for ongoing clinical trials within 2 calendar days of the effective date of the contract via a secure electronic file transfer. In the event that the Project Officer and the Contracting Officer determine that the volume of data is too great for electronic transfer, an alternative method shall be proposed by the Contractor and approved by the Project Officer and the

Contracting Officer. Any such alternative method of data transfer shall be completed within 10 calendar days of the effective date of the contract.

2) *Draft Initial Transition Plan*: Within 14 calendar days of the effective date of the contract, submit the Draft Initial Transition Plan for Project Officer review. This Plan shall detail the specific initial transition activities to be undertaken, provide a timeline for implementation of each transition activity, and describe the capabilities and responsibilities of Contractor staff who shall be assigned to implement the Initial Transition. The Draft Initial Transition Plan shall encompass the requirement for the Contractor to have an internet-based collaboration portal and internet data collection and verification systems in place for all ITN studies, including systems for both the clinical AE database and the pharmacovigilance SAE database, no later than 60 calendar days of the effective date of the contract.

   For both data transfer for clinical trials and collaborative portals, first priority shall be given to high-priority studies as determined by the Project Officer; second priority shall be given to studies open to enrollment; third priority shall be given to studies in development and nearing finalization; and last priority shall be given to closed studies and those in early development. In addition, the Draft Initial Transition Plan shall encompass the requirement for the Contractor to be capable of performing data mining and analysis on transferred datasets within this time frame.

   The Project Officer will review and provide comments on the Draft Initial Transition Plan within 7 calendar days of receipt of the Draft Plan.

3) *Final Initial Transition Plan*: Revise the Draft Initial Transition Plan in accordance with Project Officer comments, and submit the Final Initial Transition Plan within 7 calendar days of receipt of Project Officer comments.

B. Final Transition:

The Contractor shall ensure an orderly, secure and efficient transition of contract-generated data, protocol-related documents and other materials to a successor contractor or to the Government. This shall include the following:

1) *Draft Final Transition Plan*: No later than 12 months prior to the completion date of the contract, prepare and submit, for Project Officer review, a Draft Final Transition Plan. The Draft Final Transition Plan shall detail the transition activities to be carried out, provide a timeline for the implementation of each transition activity, and. describe the capabilities and responsibilities of Contractor staff who shall be assigned to implement the Initial Transition. Contract-generated materials and data to be transitioned shall include the following:

   a. Clean, edited public use dataset (including cleaned data with or without images, raw data if cleaned data is not available) and copies of all data management tools, including data documentation, data dictionaries and data entry software and editing programs to allow reading and analysis of the data for all studies managed or analyzed under the contract, including:

i. all computer programs used for reading, cleaning, manipulating, graphing and analyzing data and programs used for generating new datasets;
ii. audit trails of all data corrections, hard copies of the original data, if collected under this contract, and all logs and records related to data collection, entry, editing, verification, analysis and transfer;
iii. final summaries of analyses performed during the contract period;
iv. all electronic files transferred in and documentation of format to a location specified by the Project Officer by the contract completion date; and
v. all hard copy files, including all reports submitted to DAIT in an organized manner, providing clear documentation of contents, date of origin, and purpose to a location specified by the Project Officer prior to contract completion.

2) *Final Transition Plan*: Within 6 months prior to the completion date of the contract, submit the Final Transition Plan, revised as necessary to accommodate Project Officer comments.

3) Maintain full operational capacity until the completion date of the contract.

PART B: ASTHMA AND ALLERGIC DISEASES COOPERATIVE RESEARCH CENTERS STATISTICAL AND DATA COORDINATING CENTER SUPPORT SERVICES

The SDCC shall provide the following services for clinical research studies conducted by the NIAID AADCRC upon the request of the Project Officer and confirmation from the protocol-specific NIAID Medical Officer. These studies include research conducted with human subjects or on material of human origin such as tissues, specimens to evaluate mechanisms of human disease, therapeutic interventions, clinical trials, and development of new technologies.

1. Statistical Design

a. *Concept Proposals*: Perform feasibility assessments of Concept Proposals submitted by AADCRC Principal Investigators for evaluation by the AADCRC Steering Committee. This includes assessing feasibility with respect to the following features: (i) study design; (ii) sample size; (iii) number of cohorts and number of study participants per cohort; (iv) eligibility criteria; (iv) primary and secondary endpoints; and (v) selection of optimal randomization ratios.

b. *Clinical Protocols, Mechanistic and Surrogate/Biomarker Studies*: Review experimental study designs and statistical analysis plans for final draft protocols approved for implementation by the AADCRCs and provide recommendations for improvements and modifications to ensure appropriateness of control/comparison groups, inclusion and exclusion criteria, sample size and power estimates, primary and secondary endpoints, and randomization and stratification/blocking methods. The studies that require statistical evaluation include:

1) Mechanisms of asthma and allergic diseases

2) Therapeutic interventions e.g., environmental remediation, such as removing cockroach and house dust mites; using a HEPA filter system to minimize allergen exposure and then measuring the effect of these actions
3) Clinical Trials
4) Development of new technologies to assist in the diagnosis and treatment of asthma and allergic diseases.

These evaluations shall include the techniques and methods to delineate underlying mechanisms and to identify and validate surrogate/biomarkers for the immunologic mechanisms underlying the onset and progression of asthma and allergic diseases. In carrying out these support services, a SDCC statistician shall be assigned to each team responsible for developing the clinical protocol including statistical analysis plans for both clinical and mechanistic endpoints in each study.

2. Statistical Analyses and Final Study Reports

a. *Interim Statistical Analyses*: Perform no more than one interim statistical and trend analysis per study of clinical research study data, including the design and presentation of tables, listings, and graphical figures, for the evaluation of ongoing studies with respect to safety, toxicity, pharmacokinetics, pharmacology, efficacy, and/or exploratory mechanistic endpoints.

b. *Final Statistical Analyses*: Perform and/or review final statistical analyses of clinical research study data, including descriptive as well as univariate and multivariate inferential analyses, in accordance with the approved statistical analysis plans and based on final data set analyses provided by the AADCRC Principal Investigator responsible for each clinical protocol.

PART C: SDCC REQUIREMENTS FOR SUPPORT OF BOTH THE NIAID IMMUNE TOLERANCE NETWORK AND ASTHMA AND ALLERGIC DISEASES COOPERATIVE RESEARCH CENTERS

1. Scientific and Technical Personnel

Provide and maintain qualified scientific and technical personnel necessary to carry out the functions specified in the Statement of Work, including:

A. *Principal Investigator (PI)*: A Ph.D. statistician experienced in:
   a. statistical design, development, implementation, and analysis of Phase I, II, III, and IV clinical trials to evaluate the safety and efficacy of experimental treatment and prevention approaches, including approaches for the treatment and prevention of immune-mediated diseases;
   b. management, coordination, and oversight of the statistical design and analysis components of pre-IND and IND submissions to regulatory authorities, including interacting with the Food and Drug Administration (FDA) and other regulatory authorities on pre- and post-IND submission requirements and deliberations;
   c. design, management, and oversight of computer-based systems and databases for (i) the collection, storage, management, tracking and archiving of clinical and laboratory

data; (ii) the collection and storage of data for safety oversight and reporting; and (iii) the provision of quality control of all clinical, laboratory and safety data;

d. management and coordination of safety oversight and reporting functions involving human subjects, including preparation of safety data analyses, and presentations to and interactions with safety oversight structures and regulatory authorities;
e. coordination of statistical and data coordinating center functions in support of clinical trial networks and with other organizations providing regulatory, clinical site monitoring, and drug distribution services; and
f. working with government sponsors, government-supported clinical investigators and clinical trial networks, and industry collaborators in protocol design, development, execution, oversight, analysis and reporting.

B. *Other Scientific and Technical Personnel*:

1) *Statisticians* to evaluate concept proposals, assist in the development of statistical design and analysis plans for clinical protocols, and prepare interim and final analyses of study data.

2) *Protocol Development Personnel* with expertise in: medical writing for the development of clinical protocols, protocol-related documents, and regulatory submissions; pharmacology; toxicology; and pharmacokinetics.

3) *Chemistry, Manufacturing and Control Personnel* for the preparation and/or evaluation of manufacturing procedures and methods for generating investigational products.

4) *Safety Oversight Personnel*: Physicians and other clinical experts to carry out safety oversight functions, including the evaluation of AEs and SAEs, and to perform data cleaning and reconciliation between the clinical Adverse Event (AE) database and the pharmacovigilence (PGV) Serious Adverse Event (SAE) database maintained by the SDCC.

5) *Database and Website Design and Management Personnel* for the development and operation of computer-based systems and plans and procedures for clinical trial data collection, entry and quality control, for assessing the capabilities of and providing training for clinical sites, and for the design and maintenance of clinical study websites.

2. Project Management

A. *Overall Project Management*: Provide for the following:

1) The overall management, integration and coordination of all contract activities, including a technical and administrative infrastructure to ensure the efficient planning, initiation, implementation and timely completion of all activities carried out under this contract.
2) Effective communications with the Project Officer and the Contracting Officer.

3) A PI with responsibility for overall project management and communications, tracking performance and cost, monitoring and reporting on project status and progress, and recommending modifications to project requirements and timelines, including activities undertaken by subcontractors.
4) Effective and efficient coordination of specified functions in collaboration with the Project Officer, other DAIT staff, the ITN and AADRC Steering Committees, other DAIT clinical research support services contractors, and ITN- and AADCRC-supported investigators and clinical and laboratory site personnel.
5) At the request of the Project Officer, prepare and submit reports documenting SDCC performance as measured by the timely disposition of AE and SAE Reports (e.g., time from receipt to entry into the central database, time from receipt to reporting to health authority(ies) where applicable, and projected costs to complete the contract on a year to year basis).

B. *Meetings and Teleconferences*:

1) Contract Initiation Meeting: Within 10 calendar days of the effective date of the contract, participate in a one-day Contract Initiation Meeting with the Project Officer, the Contracting Officer and other DAIT personnel designated by the Project Officer, to be held in the Bethesda, MD area. The purpose of the Contract Initiation Meeting shall be to:

   a. introduce Contractor and DAIT staff;
   b. discuss the terms and conditions of the contract;
   c. review transition plans and activities and materials to be prepared and submitted within the first 3 months of the contract period of performance; and
   d. establish priorities and timelines for specific activities.

2) Weekly Protocol Status Teleconferences: Participate in weekly teleconferences with the Project Office and other DAIT staff, designated by the Project Officer, to discuss the status of ongoing clinical trials and clinical trials in development, identify and develop approaches to resolving problems encountered in study design, initiation and conduct with respect to SDCC responsibilities, and review plans for the design and initiation of recently approved clinical trials.

3) Site Visits: The Project Officer and the Contracting Officer may elect to conduct site visits to the Contractor's facilities or request Contractor participation in reverse site visits at any time during the contract period of performance. At a minimum, one joint site visit shall be conducted in each year by the Project Officer and the Contracting Officer.

4) ITN Steering Committee Meetings: The PI and up to three SDCC senior statistical, data management, and safety oversight staff shall attend 3 ITN Steering Committee Meetings per year.

C. *Publications and Presentations of Contract-Generated Data*:

1) The Contractor shall not publish, present or disseminate any data or other information resulting from work performed under this contract without submission of materials to the Project Officer for review and approval.

2) The Project Officer shall comment on abstracts and presentations within 7 calendar days of receipt and within 30 calendar days of receipt for publications. If the Project Officer does not respond within these time frames, the Contractor may proceed with such publications or presentations.

PART D: OPTIONS

In addition to the tasks delineated above to be provided for the basic requirement, Options for the continuation of the basic requirement and for additional tasks under the contract may be exercised by the Government and are defined as follows:

Option 1: Extension of Base Period of Performance - Under Option 1, the Government may extend the contract for one additional year beyond the contract base period of performance. If this option is exercised, the services required under this option shall be of the same scope provided for in the basic requirement for both the ITN and the AADCRCs.

Option 2: Provision of Additional SDCC Support Services for the NIAID Asthma and Allergic Diseases Cooperative Research Centers (AADCRCs)

Option 2 provides for an expansion in the scope of SDCC support services to be provided to include the collection, storage, management, quality control and reporting of data for clinical research studies conducted by the NIAID AADCRCs. Under this option, the SDCC shall be responsible for operating and managing a state-of-the-art computer-based system at a central facility for the collection, storage, management, tracking, retrieval, and quality control of all clinical, laboratory, and mechanistic data and for the management and reporting of data for all AADCRC clinical research studies, including preparation and annual review of manuals and procedures documenting data collection, editing and validation procedures and standards.

The computer-based system shall have the following features and capabilities:

a. Receive, enter, verify, label, process, edit (including within and across form validity, logic and consistency checks), update, correct, freeze, lock, store, secure, track and retrieve all clinical, laboratory, and mechanistic data at a central data management facility.
b. Computerized study forms and systems for remote data entry and transmission via the internet of subject data from study sites and laboratories to the central data management facility or non-computerized methods, such as paper Case Report Forms (CRFs), as designated by the Project Officer.
c. Comply with all current Federal regulations (§21 CFR 11 and/or similar statutes (http://www.fda.gov/cber/guidelines.htm) and meet current globally-accepted standards, including International Conference on Harmonization (ICH) E-2, Clinical Safety Data Management, and ICH M-5, Data Elements and Standards for Drug Dictionaries (http://www.ich.org/cache/compo/475-272-1.html and http://www.ich.org/cache/compo/2196-272-1.html).

d. Central computerized registration and randomization of subjects or non-computerized registration and randomization methods.
e. Real-time electronic notification to the Project Officer and his/her designees in the event that one or more protocol-specific or NIAID safety review committee-specific data trigger halting rules.
f. Generation of monthly reports on accrual and study status.

The SDCC shall also be responsible for operating and maintaining a computer-based quality control system to monitor the accuracy, completeness and timeliness of data submitted by study sites at each stage of a study. Quality control for clinical studies shall begin with study initiation/patient enrollment and proceed to the generation of final data sets. The quality control system shall provide for verification of 100 percent of study data and shall have the following features and capabilities:

a. Computerized validation and error-checking (e.g., range checks, user logics) to evaluate and improve the accuracy, timeliness and completeness of data submitted by study sites.
b. Methods and standard operating procedures to ensure uniform standardized data collection and appropriate implementation of multi-center studies across participating study sites.
c. Evaluation of quality assurance data generated for all clinical studies.
d. A computerized data query system to notify and request resolution from clinical and laboratory sites when aberrant and/or missing data are identified.

Under Option 2, the Contractor shall also be required to plan and implement an orderly, efficient and secure transition of contract-generated data, protocol-related documents and other materials to the Government or to a successor contractor. This shall include the following:

1. *Draft Final Transition Plan*: No later than 12 months prior to the completion date of the contract, prepare and submit, for Project Officer review, a Draft Final Transition Plan. The Draft Final Transition Plan shall detail the transition activities to be carried out, provide a timeline for the implementation of each transition activity, and describe the capabilities and responsibilities of Contractor staff who shall be assigned to implement the Final Transition Plan. Contract-generated materials and data to be transitioned shall include the following:

    a. Clean, edited public use dataset (including cleaned data with or without images, raw data if cleaned data is not available) and copies of all data management tools, including data documentation, data dictionaries and data entry software and editing programs to allow reading and analysis of the data for all studies managed or analyzed under the contract, including:

        i. all computer programs used for reading, cleaning, manipulating, graphing and analyzing data and programs used for generating new datasets;
        ii. audit trails of all data corrections, hard copies of the original data, if collected under this contract, and all logs and records related to data collection, entry, editing, verification, analysis and transfer;

iii. final summaries of analyses performed during the contract period;
iv. all electronic files transferred in and documentation of format to a location specified by the Project Officer by the contract completion date; and
v. all hard copy files, including all reports submitted to DAIT in an organized manner, providing clear documentation of contents, date of origin, and purpose to a location specified by the Project Officer prior to contract completion.

2. *Final Transition Plan*: No later than 6 months prior to the completion date of the contract, submit the Final Transition Plan, revised as necessary to accommodate Project Officer comments.

3. Maintain full operational capacity until the completion date of the contract.

If the Government elects to exercise Option 2, the Contractor shall provide the following:

Draft Option 2 Implementation Plan: Within 21 calendar days of exercise of Option 2, develop and submit, for review by the Project Officer and the Contracting Officer, a plan for the implementation of Option 2, including:

(1) a description of all services to be provided with detailed proposed plans and procedures for the establishment and operation of computerized systems to collect, store, manage, provide quality control and report clinical and laboratory data for Phase I and Phase II clinical trials conducted by the NIAID AADCRCs, and a timeline for the initiation and completion of each activity delineated in the plans;
(2) a description of how the additional work will be staffed, organized and managed, including a detailed description of the responsibilities and percent effort for all proposed personnel, documentation of their education, training, expertise, experience and qualifications, and an administrative framework indicating clear lines of authority and responsibility for all personnel including proposed subcontractors and consultants.
(3) a detailed description of facilities, equipment and other resources to be made available to provide the additional support services specified, and documentation of the availability of all such facilities, equipment and other resources for the entire period of performance.
(4) documentation of compliance with all current Federal regulations and capacity to meet current globally-accepted standards, including International Conference on Harmonization (ICH) E-2, Clinical Safety Data Management, and ICH M-5, Data Elements and Standards for Drug Dictionaries.
(5) a proposed Final Transition Plan.

Final Option 2 Implementation Plan: The Project Officer and the Contracting Officer will review and provide comments within 7 calendar days of receipt of the Draft Option 2 Implementation Plan. The Contractor shall revise the Draft Option 2 Implementation Plan to address comments and modifications from the Project Officer and the Contracting Officer, and submit the Final Option 2 Implementation Plan within 15 calendar days of receipt of comments.

Based on the recommendation of the Project Officer to implement Option 2, the Contracting Officer will authorize the exercise of this Option through a contract modification. The Contractor shall be required to implement Option 2 and be fully operational within 3 months of receipt of the contract modification.

Option 3: Provision of SDCC Support Services for Additional DAIT Clinical Trial Programs and Projects

Option 3 provides for an expansion in the DAIT-supported clinical trial programs and projects for which SDCC support services shall be provided. This includes existing and future programs and projects involving the design, conduct and analysis of Phase I, II and III clinical trials to evaluate the safety and efficacy of a broad range of experimental interventions for the treatment and prevention of immune-mediated disorders, including asthma and allergic diseases, autoimmune diseases, and solid organ, cell and tissue transplantation. Under this option, SDCC support services may be provided for: (i) currently funded clinical research programs/networks; (ii) future clinical research programs/networks to be supported by DAIT; and (iii) currently funded and future individual research projects.

The range of SDCC support services that may be provided under Option 3 includes any or all of the following tasks as specified in the Statement of Work for the base period:

1. Statistical design and analysis (SOW item 1)
2. Protocol development (SOW item 2)
3. Protocol-related documents and materials (SOW item 3)
4. Regulatory submissions (SOW item 4)
5. Data collection storage, management, quality control and reporting (SOW item 5)
6. Safety oversight and reporting (SOW item 6)
7. Clinical study internet-based collaboration portals (SOW item 7)
8. Study communications, collaboration and reporting (SOW item 8)
9. Clinical site training, assessment and technical assistance (SOW item 9)

If the Government elects to exercise Option 3, the Contractor shall provide the following:

Draft Option 3 Implementation Plan: Within 21 calendar days of exercise of Option 3, develop and submit, for review by the Project Officer and the Contracting Officer, a plan for the implementation of Option 3 including:

(1) a description of all services to be provided with detailed proposed plans and procedures for the provision of the support services delineated in items 1 through 9 above, and a timeline for the initiation and completion of each activity delineated in the plans;
(2) a description of how the additional work will be staffed, organized and managed, including a detailed description of the responsibilities and percent effort for all proposed personnel, documentation of their education, training, expertise, experience and qualifications, and an administrative framework indicating clear lines of authority and responsibility for all personnel including proposed subcontractors and consultants.
(3) a detailed description of facilities, equipment and other resources to be made available to support additional DAIT-funded clinical research

programs/networks and projects, and documentation of the availability of all such facilities, equipment and other resources for the entire period of performance.

Final Option 3 Implementation Plan: The Project Officer and the Contracting Officer will review and provide comments within 7 calendar days of receipt of the Draft Option 3 Implementation Plan. The Contractor shall revise the Draft Option 3 Implementation Plan to address comments and modifications from the Project Officer and the Contracting Officer, and submit the Final Option 3 Implementation Plan within 15 calendar days of receipt of comments.

Based on the recommendation of the Project Officer to implement Option 3, the Contracting Officer will authorize the exercise of this Option through a contract modification. The Contractor shall be required implement Option 3 and be fully operational within 3 months of receipt of the contract modification.

ATTACHMENT 3: REPORTING REQUIREMENTS AND DELIVERABLES

STATISTICAL AND DATA COORDINATING CENTER (SDCC):
NIAID IMMUNE TOLERANCE NETWORK AND
ASTHMA AND ALLERGIC DISEASES COOPERATIVE RESEARCH CENTERS
RFP NIH-NIAID-DAIT-08-10

ARTICLE C.2. REPORTING REQUIREMENTS

All reports required herein shall be submitted in electronic format. In addition, an original hardcopy of each report shall be submitted to the Contracting Officer and one (1) hardcopy to the Project Officer unless otherwise specified.

a. Technical Reports

In addition to those reports required by the other terms of this contract, the Contractor shall prepare and submit the following reports in the manner stated below and in accordance with the DELIVERIES ARTICLE in SECTION F.

The Contractor shall submit to the Contracting Officer and to the Project Officer technical progress reports covering the work accomplished during each reporting period. These reports are subject to technical inspection and requests for clarification by the Project Officer. These reports shall be brief and factual and prepared in accordance with the format described below.

Format of Cover page: All reports shall include a cover page prepared in accordance with the following format:

- Contract Number and Project Title
- Period of Performance Being Reported
- Contractor's Name and Address
- Author(s)
- Date of Submission
- Delivery Address

☒ (1) Quarterly Progress Report

(a) This report shall include a description of the activities during the reporting period and the activities planned for the ensuing reporting period. The first reporting period consists of the first full three months of performance including any fractional part of the initial month. Thereafter, the reporting period shall consist of three full calendar months.

(b) A Quarterly Progress Report shall be due when the Annual Progress Report is due.

(c) The Quarterly Progress Report shall include the following sections:

A. Part A: Immune Tolerance Network Statistical And Data Coordinating Center Support Services

1) *Executive Summary*: A section (not to exceed 10 pages in length) describing and updating the main activities of the SDCC with

respect to the Immune Tolerance Network during the reporting period with attention to significant progress and any major changes made to:

a. the core organizational structure of the SDCC, including study management teams for each ITN clinical trial;
b. the development, launch, execution, or close-out of any domestic or non-domestic ITN clinical trial, including major problems encountered and SDCC recommendations and actions taken to address and/or correct these problems;
c. SDCC assessments, processes, and recommendations for enhancing efficiency and quality improvement in managing the portfolio of clinical trials to address problems and develop solutions for biostatistics, programming, data management, safety oversight, medical writing, and/or information technology issues on an ongoing basis;
d. the SDCC biostatistical, data management, and safety oversight teams, including SDCC participation in review and feasibility assessments of ITN concept proposals, full applications, and the development of new protocols, protocol amendments, statistical analysis plans, CRF development, database validation, data processing and cleaning, data management reports delivery, and results of safety oversight reviews of all life-threatening (grade 4 or higher) or deaths reported as SAEs during the reporting period;
e. safety oversight structures, including both planned and *ad hoc* reviews; and
f. plans for the next reporting period, regarding study closeouts, database locks, dataset analyses, dataset transfers, interim statistical analyses, final statistical analyses, interim study reports, publications, and/or scientific presentations.

2) *Introduction*: A section covering the purpose and scope of the contract effort.

3) *Progress Report*: A section describing the overall progress for each task or segment of work listed in the Statement of Work on which effort was expended during the reporting period. The report shall include the following items:
   a. *Table of Contents*: A table listing of each ITN protocol by protocol number and protocol chair full name with page location within the progress report, organized by therapeutic category/disease area (i.e., Allergy and Asthma, Transplant, Autoimmune, Assay, and Core).
   b. *Summary Page* for the work performed for each protocol: Present a one to two page table for each ITN protocol that summarizes:
      i. Status of the project (in development, open and enrolling, on clinical hold, completed and in follow-up, completed and close, or terminated);
      ii. Analytic and/or data reporting activities in progress for the project;

iii. Ongoing challenges to the project including updates from biostatistics, data management, safety oversight, and medical writing;
iv. Action items to be addressed per project, including data collection, query resolution, and data cleaning progress for planned or *ad hoc* interim and/or final data analyses per protocol; safety reporting issues for domestic or non-domestic protocols; interim conditional statistical power analyses; and protocol amendments required to address poor enrollment or other challenges to complete a trial;
v. Current enrollment metrics, including target or actual study launch date, target sample size, number of candidates screened, and number of participants enrolled;
vi. Date of the next pending NIAID data safety review;
vii. Data management metrics, including number of participants with one or more CRFs received at the data center, number of sites with enrolled participants, number of outstanding data queries open, number of data queries greater than 28 days old, and total number of data queries resolved over the last 28 days;
viii. Safety oversight metrics: A listings of all grade 4 or higher SAEs per trial arranged by calendar date of the event and including event term, expedited or non-expedited, and event resolved medically (yes or no); and
ix. Major work performed in support of pending regulatory submission(s) activities, including the status of clinical and/or statistical documents prepared for pre-IND, IND, and annual report submissions for each project.

c. *Collaboration Portal Activities*:
   i. Describe the number of operational web sites and web pages associated with the collaboration portal.
   ii. A section listing all reports posted to the collaboration portal during the reporting period, including a listing of the following full reports:
      1. Monthly Reports:
         a. Missing Pages Report
         b. Protocol Deviation Report
      2. Quarterly Reports:
         a. Adverse Events (AE)
         b. Adverse Events Coded (AE Coded)
         c. Serious Adverse Events (SAE)
         d. Concomitant Medications (ConMed)
         e. Concomitant Medications Coded (ConMed Coded)
         f. Immunosuppressive Medications
         g. Immunosuppressive Medications Coded
         h. Treatment of Rejection
         i. Treatment of Rejection (Coded)
d. *Training*: Describe the number and types of training provided, including title of training, presenters, recipients, locations, and methods of training.

B. Part B: Asthma And Allergic Diseases Cooperative Research Centers (AADCRC) Statistical And Data Coordinating Center Support Services

1) *Executive Summary*: A section (not to exceed 10 pages in length) describing and updating the main activities of the SDCC with respect to the AADCRC during the reporting period with attention to significant progress and any major changes made to:
    a. the core organizational structure of the SDCC, including statisticians assigned to each AADCRC study;
    b. SDCC assessments, processes, and recommendations for enhancing efficiency and quality improvement in managing the portfolio of clinical studies to address problems and develop solutions for biostatistics, programming, and/or information technology issues on an ongoing basis;
    c. the SDCC biostatistical teams, including SDCC participation in review and feasibility assessments of concept proposals, the development of new protocols, mechanistic and surrogate/biomarker studies, and statistical analysis plans;
    d. the receipt, preparation, analysis, and export of protocol-specific datasets to AADCRC investigators for submission to safety oversight committees, including both planned and *ad hoc* reviews; and
    e. plans for the next reporting period, regarding dataset analyses, dataset transfers, interim statistical analyses, final statistical analyses, interim study reports, and final study reports.

2) *Introduction*: A section covering the purpose and scope of the contract effort.

3) *Progress Report*: A section describing the overall progress for each task or segment of work listed in the Statement of Work on which effort was expended during the reporting period. The report shall include the following items:

    a. *Table of Contents*: A table listing of each AADCRC protocol by protocol number and protocol chair full name with page location within the progress report, organized by therapeutic category/disease area (i.e., Food Allergy, Asthma, and Autoimmune).
    b. *Summary Page* for the work performed for each protocol: Present a one to two page table for each AADCRC protocol that summarizes:
        i. Status of the project (in development, open and enrolling, on clinical hold, completed and in follow-up, completed and close, or terminated);
        ii. Analytic and/or data reporting activities in progress for the project;
        iii. Ongoing challenges to the project including updates from biostatistics;
        iv. Action items to be addressed per project, including planned or *ad hoc* interim and/or final data analyses per protocol, and interim conditional statistical power analyses;

v. Current enrollment metrics, including target or actual study launch date, target sample size, number of candidates screened, and number of participants enrolled;
vi. Date of the next pending NIAID data safety review;

C. Problems and Solutions: A section describing technical or performance problems encountered and corrective action taken. An explanation of any differences between planned and actual progress shall be included, along with the estimated costs for resolution.

D. Financial report: A section describing the financial status of the contract, including spending for each protocol as well as a breakdown of expenditures for each protocol, including: personnel (number of hours expended for each study and cumulative overall), consultants (identify specific protocol and role), materials and supplies, equipment (specify), staff travel (identify protocol and purpose of travel), other direct costs.

☒ (2) Annual Progress Report

This report includes a summation of the results of the entire contract work for the period covered. An Annual Progress Report will not be required for the period when the Final Report is due. A ☒ Quarterly Progress Report shall be submitted when an Annual Progress Report is due. The report shall summarize the activities in progress and completed in the preceding twelve months and shall include a summary of each section provided in the Quarterly Progress Reports and any additional information pertinent to contract performance.

☒ The Contractor shall provide the Project Officer and Contracting Officer with two copies of the Annual Progress Report in **draft** form ☒ in accordance with the DELIVERIES Article in SECTION F of this contract ☒ sixty calendar days prior to the delivery date for the Final Version of the Annual Report.] The Project Officer will review the draft report and provide the Contracting Officer with comments within thirty calendar days after receipt. The Annual Progress Report shall be corrected by the Contractor, if necessary and the final version delivered as specified in the above paragraph.

☒ (3) Annual Technical Progress Report for Clinical Research Study Populations

The Contractor shall submit information about the inclusion of women and members of minority groups and their subpopulations for each study being performed under this contract. The Contractor shall submit this information in the format indicated in the attachment entitled, "Inclusion Enrollment Report," which is set forth in Section J of the contract. The Contractor also shall use this format, modified to indicate that it is a final report, for reporting purposes in the Final Report.

The Contractor shall submit the report in accordance with the DELIVERIES Article in SECTION F of this contract.

In addition, the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended, October 2001, applies. If this contract is for Phase 3 clinical trials, see II.B of these guidelines. The Guidelines may be found at the following website: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

Include a description of the plans to conduct analyses, as appropriate, by sex/gender and/or racial/ethnic groups in the clinical trial protocol as approved by the IRB, and provide a description of the progress in the conduct of these analyses, as appropriate, in the Annual Progress Report and the Final Report. If the analysis reveals no subset differences, a brief statement to that effect, indicating the subsets analyzed, will suffice. The Government strongly encourages inclusion of the results of subset analysis in all publication submissions. In the final report, the Contractor shall include all final analyses of the data on sex/gender and race/ethnicity.

☒ (4) Final Report

This report is to include a summation of the work performed and the results obtained for the entire contract period of performance. This report shall be in sufficient detail to describe comprehensively the results achieved. The Final Report shall be submitted in accordance with the DELIVERIES Article in SECTION F of the contract. An Annual Progress Report will not be required for the period when the Final Report is due.

☒ The Contractor shall provide the Project Officer and Contracting Officer with two copies of the Final Report in **draft** form ☒ in accordance with the DELIVERIES Article in SECTION F of this contract ☒ one hundred-twenty calendar days prior to the completion date of this contract. The Project Officer will review the draft report and provide the Contracting Officer with comments within thirty calendar days after receipt. The Final Report shall be corrected by the Contractor, if necessary and the final version delivered as specified in the above paragraph.

☒ (5) Summary of Salient Results

The Contractor shall submit, with the Final Report, a summary (not to exceed 200 words) of salient results achieved during the performance of the contract.

b. Other Reports and Deliverables

In addition to the above reports, the following are considered other reports and deliverables under this contract and are identified in the Statement of Work. A listing is included in the DELIVERIES Article in SECTION F.

☐ **Human Subjects IRB Annual Report** (Form OMB No. 0990-0263-formerly Optional Form 310)

☐ **Invention Report Requirement**

☒ **Source Code and Object Code**

Unless otherwise specified herein, the Contractor shall deliver to the Government, upon the expiration date of the contract, all source code and object code developed, modified, and/or enhanced under this contract.

System Security Plan

The Contractor shall submit a **System Security Plan (SSP)** that describes the management, operation, and technical controls of the computer-based system(s). Updates to the SSP must be submitted following changes to the system infrastructure.

SECTION D – PACKAGING, MARKING, AND SHIPPING

☐ Cannot be determined at this time
☐ Temperature controlled environment is required
☐ Shipments will be time sensitive/time critical
☐ International shipping will apply
☐ Shipping insurance is required
☐ Hazardous Materials shipping is applicable
☐ Other (list as necessary) _____
☒ N/A to this solicitation

ARTICLE F - DELIVERIES

Satisfactory performance of the final contract shall be deemed to occur upon performance of the work described in the STATEMENT OF WORK Article in SECTION C of this contract and upon delivery and acceptance by the Contracting Officer, or the duly authorized representative, of the following items in accordance with the stated delivery schedule:

The items specified below as described in the REPORTING REQUIREMENTS Article in SECTION C of this contract will be required to be delivered F.o.b. Destination as set forth in FAR 52.247-35, F.o.b. DESTINATION, WITHIN CONSIGNEES PREMISES (APRIL 1984), and in accordance with and by the date(s) specified below [and any specifications stated in SECTION D, PACKAGING, MARKING AND SHIPPING, of this contract]:

a. Technical Progress Reports

Item	Reports	Recipients	Delivery Schedule
1.	Quarterly Progress Report	1 hard copy to PO 1 original to CO 1 elec. copy to PO and CO	The first report is due on/before the 15th of the month following the first reporting period consisting of the first full 3 months of performance plus any fractional part of the initial month. Thereafter, each report is due on/before the 15th of the month following the end of each 3-month reporting period.
2.	Draft Annual Progress Report	1 hard copy to PO 1 original to CO 1 elec. copy to PO and CO	Due on/before 60 calendar days prior to the delivery date of the final version. PO comments due within 30 calendar days after receipt.

Item	Reports	Recipients	Delivery Schedule
3.	Annual Progress Report	1 hard copy to PO 1 original to CO 1 elec. copy to PO and CO	Due annually on/before 30 calendar days following the anniversary date of the contract. The Quarterly Progress Report is to be submitted when the Annual Progress Report is due.
4.	Annual Technical Progress Report for Clinical Research Study Populations	3 hard copies to PO 1 original to CO 1 elec. copy to PO and CO	Due annually on/before 30 calendar days following the anniversary date of the contract.
5.	Draft Final Report	1 hard copy to PO 1 original to CO 1 elec. copy to PO and CO	Draft Final Report is due 120 calendar days prior to the delivery date of the final version. PO comments due within 30 calendar days after receipt.
6.	Final Report	1 hard copy to PO 1 original to CO 1 elec. copy to PO and CO	Final Report is due on/before the completion date of contract.

b. Other Reports and Deliverables (Delivery Schedule)

Item	Deliverables	SOW Reference	Recipient	Delivery Schedule
1.	Draft Interim Analysis	Part A, Item 1.B.1	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	Within 14 calendar days of analysis completion.
2.	Final Interim Analysis	Part A, Item 1.B.1 Part B, Item 2.A	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	Within 14 calendar days of receiving PO comments.
3.	Draft Final Statistical Analysis Report	Part A, Item 1.B.2	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	Within 30 calendar days of completion of final data set.
4.	Final Statistical Analysis Report	Part A, Item 1.B.2 Part B, Item 2.B	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	Within 30 calendar days of receiving PO comments.

Item	Deliverables	SOW Reference	Recipient	Delivery Schedule
5.	Listings of electronic data transfers	Part A, Item 1.B.3	1 hard copy to PO; 1 elec. copy to PO	Quarterly; due on/before the 15th of the month following the end of each 3-month reporting period.
6.	IND applications and pre-IND briefing packets	Part A, Item 4.A	1 hard copy to PO; 1 hard copy to NIAID Regulatory Officer; 1 elec. copy to PO and NIAID Regulatory Officer	To be specified by PO.
7.	Written and oral materials for presentations to the FDA	Part A, Item 4.B	1 hard copy to PO; 1 hard copy to NIAID Regulatory Officer; 1 elec. copy to PO and NIAID Regulatory Officer	To be specified by PO.
8.	Interim Clinical Study Report	Part A, Item 4.E	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	To be specified by PO.
9.	Draft Systems Plan	Part A, Item 5	1 hard copy to PO; 1 elec. copy to PO	Due on/before 15 calendar days of the effective date of contract. PO comments due within 15 calendar days after receipt.
10.	Final Systems Plan	Part A, Item 5	1 hard copy to PO; 1 elec. copy to PO	Due on/before 60 calendar days of the effective date of contract.
11.	Written assessments and recommendations for enhancements to Database I and II	Part A, Item 5.C.5	1 hard copy to PO; 1 elec. copy to PO	To be specified by PO.
12.	Revised Manuals and Data Collection Procedures	Part A, Item 5.C.7	1 hard copy to PO; 1 elec. copy to PO	Due annually on/before 30 calendar days following the anniversary date of the contract.
13.	System Security Plan	Part A, Item 5.D.2	1 hard copy to PO; 1 elec. copy to PO, CO and NIAID Information System Security Officer (ISSO)	Due within 90 calendar days of the effective date of the contract. Updates due within 30 calendar days of change to system infrastructure.

Item	Deliverables	SOW Reference	Recipient	Delivery Schedule
14.	Information System Security Plan (ISSP)	Part A, Item 5.D.3	1 hard copy to PO; 1 hard copy to NIAID Information System Security Officer (ISSO); 1 elec. copy to PO and NIAID Information System Security Officer (ISSO)	Due on/before 20 calendar days of the effective date of contract. Thereafter, due annually on/before 30 calendar days following the anniversary date of the contract.
15.	Risk Analysis	Part A, Item 5.D.5	1 hard copy to PO; 1 hard copy to NIAID Information System Security Officer (ISSO); 1 elec. copy to PO and NIAID Information System Security Officer (ISSO)	Due on/before 20 calendar days of the effective date of contract. Thereafter, due every 3 years on/before 30 calendar days following the anniversary date of the contract.
16.	Interim Analyses and Oral Presentations	Part A, Item 6.B.3	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	Due on/before 21 calendar days of scheduled meetings with NIAID Safety Oversight Structures.
17.	Final Materials for NIAID Safety Oversight Structures	Part A, Item 6.B.3	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; Hard copies to each DSBM member; 1 elec. copy to PO, NIAID Medical Monitor, and DSMB members	Due on/before 14 calendar days prior to scheduled meetings or teleconferences.
18.	Draft written summaries of deliberations of NIAID Safety Oversight Structures	Part A, Item 6.B.4	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	Due on/before 7 calendar days of completion of meetings with NIAID Safety Oversight Structures.

Item	Deliverables	SOW Reference	Recipient	Delivery Schedule
19.	Final written summaries of deliberations of NIAID Safety Oversight Structures	Part A, Item 6.B.4	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	Due on/before 5 calendar days of receipt of Medical Monitor comments.
20.	Written summaries documenting recommendation from NIAID Safety Oversight Structures	Part A, Item 6.B.4	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	Due on/before 2 calendar days of completion of meetings with NIAID Safety Oversight Structures.
21.	Written responses to recommendations of NIAID Safety Oversight Structures	Part A, Item 6.B.5	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	To be specified by PO.
22.	Protocol-specific AE and SAE Reporting Forms and Instructions	Part A, Item 6.C.2	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	Due on/before 15 calendar days of completion of each Final Protocol
23.	Study Site Performance Report	Part A, Item 6.C.7	1 hard copy to PO; 1 hard copy to NIAID Medical Monitor; 1 elec. copy to PO and NIAID Medical Monitor	Due annually on/before 30 calendar days following the anniversary date of the contract.
24.	Draft Collaboration Portal Plan	Part A, Item 7.C	1 hard copy to PO; 1 elec. copy to PO	Due on/before 30 calendar days of the effective date of contact.
25.	Final Collaboration Portal Plan	Part A, Item 7.C	1 hard copy to PO; 1 elec. copy to PO	Due on/before 10 calendar days of receipt of PO comments.
26.	SDCC Internet Data Entry System User's Manual	Part A, Item 9.A.1	1 hard copy to PO; 1 elec. copy to PO	Due on/before 60 calendar days of the effective date of contract.
27.	Clinical Site Assessment Report	Part A, Item 9.B.1	1 hard copy to PO; 1 elec. copy to PO	Due on/before 30 calendar days of completion of assessment.

Item	Deliverables	SOW Reference	Recipient	Delivery Schedule
28.	Study Site Cost Performance Report	Part C, Item 2.A.5	1 hard copy to PO; 1 elec. copy to PO	Due annually on/before 30 calendar days following the anniversary date of the contract.
29.	Draft Initial Transition Plan	Part A, Item 11.A.2	1 hard copy to PO; 1 elec. copy to PO	Due on/before 14 calendar days of effective date of contract.
30.	Final Initial Transition Plan	Part A, Item 11.A.3	1 hard copy to PO; 1 elec. copy to PO1 hard copy to PO; 1 elec. copy to PO	Due on/before 7 calendar days of receipt of PO comments.
31.	Draft Final Transition Plan	Part A, Item 11.B.1 Part D, Option 2	1 hard copy to PO; 1 elec. copy to PO	Due on/before 12 months prior to completion date of contract.
32.	Final Transition Plan	Part A, Item 11.B.2 Part D, Option 2	1 hard copy to PO; 1 elec. copy to PO	Due on/before 6 months prior to completion date of contract.
33.	Draft Implementation Plan	Part D, Option 2 Part D, Option 3	1 hard copy to PO; 1 hard copy to CO; 1 elec. copy to PO and CO	To be specified by PO, if exercised.
34.	Final Implementation Plan	Part D, Option 2 Part D, Option 3	1 hard copy to PO; 1 hard copy to CO; 1 elec. copy to PO and CO	Due on/before 15 calendar days of receipt of PO and CO comments to draft.

ATTACHMENT 4: ADDITIONAL TECHNICAL PROPOSAL INSTRUCTIONS, FORMAT FOR TECHNICAL PROPOSAL, and TABLE OF CONTENTS

Statistical and Data Coordinating Center: NIAID Immune Tolerance Network and Asthma and Allergic Diseases Cooperative Research Centers
RFP NIH-NIAID-DAIT-08-10

It is strongly recommended that offerors use the following template as the Table of Contents for the Technical Proposal. All information presented in the Technical Proposal should be presented in the order specified below.

These additional Technical Proposal instructions reflect the requirements of the RFP and provide specific instructions and formatting for the Technical Proposal. While Section L.2.b. of the RFP provides a generic set of Technical Proposal instructions applicable to all NIH R&D solicitations, these instructions are tailored to the specific requirements of the RFP. The information requested in these instructions should be used to format and prepare the Technical Proposal, and should be used as a Table of Contents for your Technical Proposal. Offerors should follow the instructions in Section L of the solicitation, and include the information requested here.

Offerors are advised to give careful consideration to the Statement of Work, all reference materials, and attachments, the Technical Evaluation Criteria in Section M, and the RFP as a whole in the development of their Technical Proposals.

Offerors proposing subcontracts to perform portions of the Statement of Work should clearly identify the specific tasks for which they plan to utilize subcontractors, as well as the method and level of integration/coordination between the prime Contractor and all proposed subcontractors, and the expected advantages of such an approach.

Offerors are reminded that the total page limitation for the entire Technical Proposal is 300 pages including all appendices and attachments. Any pages in excess of this limit will be expunged from the proposal and will not be considered in the technical review. Proposals shall NOT include links to Internet Web site addresses (URLs) or otherwise direct readers to alternate sources of information.

TECHNICAL PROPOSAL – TABLE OF CONTENTS

SECTION 1:

1) PROPOSAL TITLE PAGE. Include RFP title and number, name of organization, DUNS number, proposal part, and identify if the proposal is an original or a copy.
2) PROJECT OBJECTIVES, NIH FORM 1688
3) GOVERNMENT NOTICE FOR HANDLING PROPOSALS
4) PROPOSAL SUMMARY AND DATA RECORD (NIH-2043)
5) TABLE OF CONTENTS

SECTION 2: TECHNICAL PROPOSAL OVERVIEW (suggested maximum of 3 pages)

Provide a brief overview of the proposed Statistical and Data Coordinating Center (SDCC), including descriptions of the following:

A. The activities to be performed by the offeror and all proposed subcontractors, including the identification of proposed subcontractors and a list of key personnel of the offeror and the proposed subcontractors with degrees and titles.
B. The key features of the proposed computer-based systems for data entry and management and for safety monitoring and reporting.
C. The facilities and equipment to be made available by the offeror and all proposed subcontractors, including: the central data management facility, the Safety Reporting Center, and off-site back-up facilities.

SECTION 3: TECHNICAL PLAN/APPROACH

A. Statistical Design (Part A: SOW item 1.A and Part B: SOW item 1)

1) Describe organizational experience with and provide proposed plans and procedures for performing the following statistical design support functions:

    a. *Concept Proposals and Full Applications*: Assessing the feasibility of concept proposals and full applications for clinical trials with respect to experimental statistical design and data analysis plans. For each concept proposal or full application include the phase of the clinical trial proposed, the type of study product (e.g., therapeutic, vaccine, device), the study population/disease, period during which the feasibility assessment was conducted, and the sponsor (e.g., industry, government, private foundation, etc.). In addition, briefly discuss major problems and deficiencies encountered in performing such feasibility assessments and approaches recommended and implemented to overcome and/or minimize identified problems and deficiencies with attention to managing factors that may preclude the clinical trial from meeting its stated primary and secondary objectives.
    b. *Clinical Protocols*: Developing and refining experimental study designs and data analysis plans for clinical protocols. For each clinical protocol include the phase of the clinical trial, the type of study product, the study population/disease, sample size, number of participating study sites, overall experimental design, period during which statistical design support was provided, the status of the clinical trial, and the sponsor. In addition, briefly discuss major problems and deficiencies encountered in developing appropriate experimental designs and analysis plans and approaches recommended and implemented to overcome and/or minimize identified problems and deficiencies.
    c. *Mechanistic and Surrogate/Biomarker Studies*: Assessing the validity and reliability of techniques and methods used for studies to delineate underlying mechanisms either conducted independently or in conjunction with a clinical trial, and studies to identify and validate surrogate/biomarkers of disease susceptibility and disease stage, progression and severity. For each study provide a brief description of the techniques, methods and surrogate/biomarkers utilized and the major design features addressed with respect to validity and reliability.

In addition, briefly discuss common statistical design problems associated with such studies and approaches recommended and implemented to overcome and/or minimize identified problems.

d. *Preclinical Safety Study Evaluations*: Evaluating the statistical accuracy and validity of preclinical safety studies in support of clinical trials. For each evaluation include the type of product, disease, scope of preclinical safety study, and sponsor.

2) Discuss statistical design considerations of particular relevance and importance for evaluating hypothesis-generating versus hypothesis-testing mechanistic assays included in all ITN trials. Describe statistical approaches to optimize the yield from experimental approaches examining the induction and maintenance of immune tolerance in general and specifically for the immune-mediated diseases and patient populations which constitute the focus of the Immune Tolerance Network (ITN).

3) Discuss statistical design considerations of particular relevance and importance for evaluating hypothesis-generating versus hypothesis-testing mechanistic assays included in AADCRC clinical research studies. Describe statistical approaches to optimize the yield from experimental approaches examining the immunologic mechanisms underlying the onset and progression of asthma and allergic diseases that constitute the focus of the AADCRC projects.

B. Statistical Analysis (Part A: SOW item 1.B and Part B: SOW item 2)

Describe organizational experience with and provide proposed plans and procedures for performing the following statistical analysis functions. For clinical trials, include the phase of the clinical trial, the type of study product, the study population/disease, sample size, number of participating study sites, overall experimental design, period during which statistical analysis support was provided, and sponsor. If available publicly, also provide a brief summary of the overall findings of completed clinical trials.

1) Interim statistical and trend analyses of clinical trial data for evaluating ongoing clinical trials with respect to safety, toxicity, pharmacokinetics, pharmacology, efficacy, and/or exploratory endpoints.
2) Comprehensive final statistical analyses of all clinical trial data, including descriptive as well as univariate and multivariate inferential analyses.
3) Analyses of surrogate/biomarker studies.

C. Case Study 1: Feasibility Assessment of ITN Concept Proposal – Cytokine Production in Children with Pre-Clinical and Clinical Type 1 Insulin Dependent Diabetes Mellitus

Perform a statistical feasibility assessment of a hypothetical ITN Concept Proposal to establish assays capable of detecting the initiation of islet cell-specific immunity, the destructive capacity of this response and its natural development in children. The hypothetical Concept Proposal and specific instructions on the scope of the feasibility assessment are provided in Addendum 1 to these Additional Technical Proposal Instructions. Provide your critical analysis of this hypothetical Concept Proposal as a single document, not to exceed 10 single-

spaced pages, and place as the third component of Section 3 of the Technical Proposal.

D. Case Study 2: Feasibility Assessment of AADCRC Concept Proposal - Immune Responses to Natural Rhinovirus Infections in Individuals with Allergic Asthma, Allergic Rhinitis and Controls

Perform a statistical feasibility assessment of a hypothetical AADCRC Concept Proposal to study immune responses to natural rhinovirus infections. The hypothetical Concept Proposal and specific instructions on the scope of the feasibility assessment are provided in Addendum 2 to these Additional Technical Proposal Instructions. Provide your critical analysis of this hypothetical Concept Proposal as a single document, not to exceed 10 single-spaced pages, and place as the second component of Section 3 of the Technical Proposal.

E. Case Study 3: Feasibility Assessment of ITN Full Application – Phase II Clinical Trial of Tolerance Induction for Active Rheumatoid Arthritis

Perform a statistical feasibility assessment of a hypothetical ITN Full Application proposing a Phase II clinical trial for preliminary assessment of both clinical safety and clinical efficacy to determine whether the combined immunomodulatory properties of two drugs can increase the proportion of rheumatoid arthritis participants achieving clinical remission compared to either drug alone. The hypothetical Full Application and specific instructions on the scope of the feasibility assessment are provided in Addendum 3 to these Additional Technical Proposal Instructions. Provide your critical analysis of this hypothetical Full application as a single document, not to exceed 10 single-spaced pages, and place as the fifth component of Section 3 of the Technical Proposal.

F. Protocol Development (Part A: SOW item 2)

Describe organizational experience with and provide proposed plans and procedures for the provision of specialized support services to assist in developing the clinical, medical, pharmacological/pharmacokinetic, toxicologic, chemistry and manufacturing aspects of clinical protocols. Include a list of clinical protocols for which such specialized services have been provided and the period during which such services were provided, identify those components of the clinical protocols for which specialized services have been provided, and indicate whether support involved the independent preparation of selected protocol components or assistance to clinical investigators in the preparation of protocol components. In addition, discuss common problems and difficulties encountered in developing these aspects of clinical protocols and recommendations developed and implemented to overcome and/or reduce identified problems and difficulties.

G. Protocol-Related Documents and Materials (Part A: SOW item 3)

Describe organizational experience with and provide proposed plans and procedures for preparing and/or assisting in the preparation of protocol-related documents and materials required for implementation of clinical trials. Include the following:

1) Plans and procedures for generating electronic and paper Case Report Forms (CRFs) and examples of CRFs prepared for clinical trials relevant to the scope of research to be supported by the SDCC. (Suggested limit of 10 pages for examples of CRFs.)
2) The table of contents and Data Management section for a Manual of Operations (MOO) and a list of MOOs prepared for clinical trials relevant to the scope of research to be supported by the SDCC.
3) The table of contents for an Investigators Brochure.
4) Examples of previously generated source documents, questionnaires, memory aids, subject instructions, screening and recruitment logs, and test article accountability logs. (Suggested limit of 10 pages.)
5) Plans and procedures for reviewing, updating and distributing protocol-related materials to DAIT, study sites, and industry collaborators.

H. Regulatory Submissions (Part A: SOW item 4)

Describe organizational experience with and provide proposed plans and procedures for assisting in the following activities relating to Investigational New Drug (IND) applications submitted to the U.S. Food and Drug Administration (FDA) and other regulatory authorities. Include a general description of INDs for which support has been provided identified by the phase of the clinical trial, type of product, and the countries involved in conducting the clinical trial. This includes preparing the following:

1) Components of IND submissions relating to statistical design and analysis.
2) Components of pre-IND briefing packets relating to statistical design and analysis.
3) Written materials and oral presentations on statistical design and analysis issues/plans for meetings and teleconferences with the FDA and other regulatory authorities, and responses to inquiries on these aspects of INDs from such regulatory authorities.
4) Statistical and clinical documents required for Annual IND Reports for both ongoing and completed clinical trials.
5) Interim Clinical Study Reports at clinical trial completion to integrate clinical and statistical observations, analyses and conclusions for submission to regulatory authorities.

I. Data Management and Reporting (Part A: SOW item 5)

1) Describe the proposed computer-based systems, provide proposed plans and procedures for system implementation, operation, maintenance and the provision of quality control of all clinical and laboratory data, and describe the capacity of all proposed systems to meet features and capabilities specified in the Statement of Work. Include a discussion of the capacity of all proposed systems to comply with domestic and non-domestic regulatory requirements, including requirements of the European Union (EU), and data storage plans, including back-up procedures, disaster recovery procedures and query abilities.

    a. *Data Collection, Storage and Management (Database I)*: The computer-based system for the collection, storage, management, tracking and archiving of all clinical and laboratory data, including Adverse Events

(AEs), and for the management and reporting of data and other information for clinical trials and pre-clinical studies.

Describe system capabilities for: (i) receipt, entry, verification, labeling, processing, editing, updating, correcting, freezing, locking, storing, retrieval, and archiving of all clinical and laboratory data at a central data management facility; (ii) central computerized registration and randomization and system for off-line data entry when necessary; (iii) computerized study forms and systems for remote data entry and transmission via the internet of subject data from study sites and laboratories, and non-computerized methods when necessary; (iv) real-time electronic notification in the event that one or more protocol-specific or NIAID safety review committee-specific data trigger halting rule(s) occur; (v) compatibility with systems used by DAIT, the ITN and the Asthma and Allergic Diseases Cooperative Research Centers (AADCRCs); and (vi) daily e-mail notification for high priority clinical trials of accrual and study status.

b. *Safety Data Collection and Reporting (Database II)*: The computer-based system to monitor and report Serious Adverse Events (SAEs) for all domestic and non-domestic study sites.

Describe the number and scope of data collection systems proposed, the rationale for each, and the interaction among and between proposed data systems. Also include a description of system capabilities for the provision of an internet-based tracking system for the receipt, reporting and disposition of SAEs.

c. *Data Quality Control*:

(1) Describe proposed plans, procedures and systems to be used to provide quality control of all clinical and laboratory data (Database I) and of all SAE data (Database II) collected for clinical trials to be supported under the contract. This includes proposed plans and procedures for:

(a) Monitoring the accuracy, completeness and timeliness of 100 percent of data submitted by study sites beginning with study. initiation/enrollment and through the generation of final data sets.
(b) Providing for computerized validation and error-checking to evaluate and improve data accuracy, completeness and timeliness;
(c) Providing uniform standardized data collection and appropriate implementation of multi-center studies across participating study sites.
(d) Evaluating data derived from ongoing quality assurance checks;
(e) Manual evaluation of AE versus SAE data entries for query and resolution of the AE (Database I) and SAE (Database II) listings.
(f) A computerized data query system to notify and request resolution from clinical and laboratory sites when aberrant and/or missing data are identified.

2) Describe organizational experience with the preparation and implementation of manuals and procedures documenting data collection, editing and validation procedures and standards and provide the table of contents for

such a manual. Provide an example of a Table of Contents for a users manual.

3) Describe similar data systems designed, maintained and updated in support of clinical research programs.

J. Safety Oversight and Reporting (Part A: SOW item 6)

Describe organizational experience with and provide proposed plans and procedures for carrying out the following safety oversight and reporting functions. As appropriate for each function, include a discussion of organizational experience in terms of the scope of clinical investigators/clinical trial networks, sponsors, safety oversight structures and regulatory authorities involved.

1) *Data and Safety Monitoring Plans (DSMPs)*: Include a list of clinical trials for which DSMPs have been prepared identified by: clinical trial phase, type of study product, study population/disease, overall experimental design, sample size, number of participating study sites, type of responsible safety oversight structure, period during which support was provided, sponsor, and clinical trial status. Identify the specific responsibilities carried out with respect to the design and development of DSMPs versus responsibilities carried out by others, including clinical investigators and sponsors.

2) *NIAID Safety Oversight Structures*: Include relevant organizational experience in the following areas:

a. Arranging for the distribution and review of final draft protocols and subsequent protocol amendments by safety oversight structures, reviewing recommendations of safety oversight structures, and modifying final draft protocols as necessary to implement recommendations accepted by study sponsors.
b. Arranging for review of DSMPs by safety oversight structures during the course of ongoing clinical trials and modifying DSMPs in accordance with recommendations accepted by study sponsors.
c. Preparing separate interim analyses of blinded and unblinded study data for review at both open and closed sessions of meeting and teleconferences of safety oversight structures, including transmittal memorandum highlighting interval changes in safety, efficacy or other parameters relevant to safety oversight, preparing and making oral presentations at meetings and teleconferences of safety oversight structures to explain results of interim analysis and address questions on patient safety, and assisting in the preparation of responses to questions and recommendations from safety oversight structures.
d. Preparing written summaries of the deliberations and recommendations of safety oversight structures and assisting in preparing and coordinating communications among multiple parties to implement accepted recommendations to change an ongoing study.

3) *Safety Reporting*: Describe organizational experience with and provide proposed plans and procedures for establishing and operating a Safety Reporting Center to provide for the following functions and features:

a. An internet data entry system of collecting Adverse Event (AE)

and Serious Adverse Event (SAE) Reports from study sites and training in the use of the internet data entry system.

b. Telephone help line and on-call back-up support services.
c. Standard operating procedures for AE and SAE reporting.
d. Protocol-specific AE and SAE reporting forms, including events to be documented, clinical data to be recorded, grading and attribution.
e. Evaluation of SAE Reports and preparation and entry of abstracts of SAE Reports into the safety database.
f. Immediate notification of all SAEs to Study Management Team members.
g. Documenting and reporting on study site performance with respect to safety reporting.
h. Procedures for ensuing compliance with all regulatory requirements and Good Clinical Practice (GCP) guidelines.

In addition, discuss problems and deficiencies encountered in ensuring the accuracy, completeness and timeliness of AE and SAE reporting by study sites and recommendations developed and implemented to overcome identified problems and deficiencies.

K. Clinical Study Internet-based Collaboration Portals (Part A: SOW item 7)

Describe organizational experience with and provide proposed plans and procedures for establishing, maintaining and updating clinical study collaboration portals to house clinical trial information and study-specific documents and materials, including plans and procedures for:

1) Protocol-specific, password-protected websites.
2) Real-time standard and study-specific data by site and total overall, including accrual, AE and SAE listings, protocol deviations, missing forms, visit schedule compliance, data queries and progress monitoring information.
3) Updates to all website documents and materials and electronic notification of availability of new or revised documents and materials.

L. Study Communication, Collaboration and Reporting (Part A: SOW item 8)

1) Describe organizational experience in collaborating and coordinating with other organizations providing clinical research support services with respect to clinical site training, clinical site monitoring, and regulatory activities. Identify the organization and/or type of clinical research support provided, the activities involving coordination/collaboration, and the period during which such collaboration/coordination was carried out. Include a discussion of problems encountered in the coordination of such activities and recommendations developed and implemented to resolve identified problems.

2) Describe proposed plans and procedures for working with the DAIT Clinical Site Monitoring Group to plan for and participate in site monitoring visits; discuss organizational experience in conducting site monitoring visits to identify and verify deficiencies noted during data submission and to recommend remedial actions with attention to deficiencies identified during data submission (e.g., protocol deviations, late, incomplete, or missing CRFs,

etc.).

3) Describe proposed plans and procedures for working with the DAIT Regulatory Management Center to plan and develop materials for study initiation meetings.

4) Describe proposed plans and procedures for working with the DAIT Drug Distribution Center to assess compliance with randomization and appropriate administration of test articles and study products.

M. Clinical Site Training, Assessment and Technical Assistance (Part A: SOW item 9)

1) *Clinical Site Training*:

   a. Describe organizational experience with and provide proposed plans and procedures for developing and conducting training for clinical site personnel with respect to: (i) procedures for study implementation including MOOs, CRFs and study participant instructions; (ii) design of data collection instruments and materials; (iii) collection, entry, management, validation and quality control of study data, audit trails, and transfer of study data to the central data management facility; and (iv) use of the internet data entry system and telephone help line for safety reporting and standard and study-specific procedures and instructions for the preparation and submission of AE and SAE Reports to the Safety Reporting Center.
   b. Briefly discuss common problems and deficiencies encountered with clinical site performance in these aspects of protocol conduct and identify recommendations developed and implemented to overcome and/or resolve identified problems and deficiencies.
   c. Provide examples of the agendas, topics and presenters from previous clinical site training activities conducted and identify the training formats (e.g., face-to-face workshop, webcast, etc.), and audiences.

2) *Clinical Site Assessment and Technical Assistance*: Describe proposed plans and procedures for assessing the capabilities of ITN-supported study sites unable to utilize SDCC internet data entry and management systems to collect, enter, secure, validate, manage and submit clinical trial data. Also describe proposed plans and procedures for collaborating with the DAIT Clinical Site Monitoring Group to plan for and conduct site initiation visits to assess study site capabilities with respect to computer equipment, facilities and systems, plans and procedures of data quality control and safety reporting, and designated site personnel assigned to carry out these functions.

N. Initial Transition (Part A: SOW item 11)

Provide a proposed plan for the secure, orderly and efficient transition of clinical and laboratory data, study-related documents and materials, and other contract-generated resources from the incumbent contractor. Include plans for transferring data and other documentation for studies in development, studies currently enrolling, and studies for which enrollment has been completed. Include all data elements and, in particular, address the following:

1) Detailed plans for database transition.
2) Timelines and detailed plans to ensure a seamless transition of currently enrolling studies.
3) Plan to provide final study reports and other required regulatory reports for all studies in transition.

SECTION 4: SCIENTIFIC AND TECHNICAL PERSONNEL (Part C: SOW item 1)

The Technical Proposal should include all information relevant to document the individual education, training, expertise, experience, qualifications and percent effort of all proposed scientific and technical personnel of the offeror and all proposed subcontractors necessary for successful completion of contract requirements. Limit CVs to 2-3 pages, include relevant experience with projects of similar size and complexity, and provide selected references for publications relevant to the scope of the RFP.

1) **Principal Investigator (PI)**: Describe the education, training, expertise, experience, qualifications and percent effort of the proposed PI to lead and direct the activities to be carried out under this contract, including:
   a. statistical leadership for the design, development, implementation and analysis of all phases of clinical trials to evaluate the safety and efficacy of experimental treatment and prevention approaches, including approaches for the treatment and prevention of immune-mediated diseases.
   b. coordinating and managing statistical design and analysis components of submissions and interacting with the FDA and other regulatory authorities on pre- and post-IND submission requirements and deliberations.
   c. the design, operation and oversight of state-of-the art computer-based systems for the collection, storage, management, tracking and archiving of clinical and laboratory data, the collection and storage of data for safety oversight and reporting, and systems for ensuring quality control of clinical, laboratory and safety data.
   d. coordinating and managing safety oversight and reporting functions, including preparing and presenting safety data and analyses for safety oversight structures and regulatory authorities.
   e. coordinating statistical and data coordinating center support functions with other organizations involved in providing regulatory, clinical site monitoring, and drug distribution services.
   f. working with government sponsors, government-supported clinical investigators and clinical trial networks, and industry collaborators in protocol design, development, execution, oversight and reporting.

2) **Other Scientific and Technical Personnel**: Describe the education, training, expertise, experience, qualifications and percent effort of all other scientific and technical personnel of the offeror and all proposed subcontractors, including:
   a. statisticians
   b. protocol development personnel
   c. chemistry, manufacturing and control personnel
   d. safety oversight personnel
   e. database and website design and management personnel

SECTION 5: FACILITIES, EQUIPMENT AND OTHER RESOURCES (Part A: SOW item 10)

Provide a description and documentation of the availability and adequacy of facilities, equipment and other resources to be used for performance of the contract for the offeror and all proposed subcontractors, including:

A. The central facilities for data collection, computer processing, storage, tracking and retrieval of all study data, including the location(s) and features of the facilities and lease or ownership information.
B. The off-site facility for back-up copies of data, including the location and features of the facility and leave or ownership information.
C. The central facility to serve as the Safety Reporting Center and the telephone help line, including the location(s) and features of the facilities and lease or ownership information.
D. Computers, hardware and software, and computer equipment and servers, including a description of security systems in place.
E. Resources to ensure secure internet access.
F. Controlled access areas for secure storage of study data and confidential study information.
G. Webcast and video capability for training purposes that can be uploaded to the internet.

SECTION 6: PROJECT MANAGEMENT (Part C: SOW item 2)

A. Provide a plan for project organization, staffing and management, including a detailed description of the responsibilities for all proposed personnel who will be assigned to the contract, and an administrative framework indicating clear lines of authority and responsibility for all personnel including proposed subcontractors. The plan must include a description of the quality control methods that will be used to ensure the effective and efficient initiation, implementation, management, oversight and completion of contract requirements.
B. Describe project management and financial management systems that will be used to track activities and to keep multiple activities on time and within budget.
C. Outline how the PI will communicate and interact with the Project Officer and the Contracting Officer and how the PI will communicate, monitor and manage the project both internally and externally (at subcontractor facilities).
D. Provide a plan for soliciting, evaluating, negotiating, awarding and managing subcontracts in accordance with FAR Clause 52.244-2.
E. Describe experience and education of contract management staff in the acquisition and management of subcontracts under Federal contracts.
F. Describe experience with the identification and remediation of subcontractor performance problems or noncompliance with subcontract terms and conditions.

SECTION 7: OPTIONS (Part D)

A. *Option 2- Provision of Additional SDCC Support Services for the NIAID Asthma and Allergic Diseases Cooperative Research Centers*: Provide proposed plans and procedures to expand the scope of SDCC support to

include the collection, storage, management, quality control and reporting of data for Phase I and Phase II clinical trials conducted by the NIAID AADCRCs. Include proposed plans and procedures for the following support services and provide a description of how the additional work will be staffed, organized and managed, including the type, number, percent effort and responsibilities of all personnel of the offeror and any proposed subcontractors to be assigned to carry out the expanded support services:

1) The computer-based system for data collection, entry, storage, and management.
2) Computerized study forms and systems for remote data entry and transmission via the internet of subject data from study sites and laboratories to a central data management facility or non-computerized methods when necessary.
3) Central computerized registration and randomization of subjects or non-computerized registration and randomization methods when necessary.
4) The quality control system(s) to be used to monitor the accuracy, completeness and timeliness of data submitted by study sites at each stage of a study, providing for verification of 100 percent of study data.
5) Compliance with domestic and non-domestic regulatory requirements, including requirements of the European Union (EU), and data storage plans, including back-up procedures, disaster recovery procedures and query abilities.

B. *Option 3 – Provision of SDCC Support Services for Additional DAIT Clinical Trial Programs and Projects*: Describe how SDCC support for additional DAIT clinical trial programs and projects will be accommodated, including: (i) assessing and accommodating the need for additional scientific and technical staff within the offeror's organization and/or through subcontracts and methods to ensure that the necessary number and type of qualified and experienced of scientific and technical staff are available; (ii) expanding existing or establishing additional computer-based systems for the collection, storage, management and quality control of study data; and (iii) modifying or augmenting the SDCC management structure to accommodate oversight responsibilities to support additional programs and projects.

SECTION 8: OTHER CONSIDERATIONS

Section L of the RFP provides minimum documentation requirements for the following items. The required information described in Section L should be assembled together, in the following clearly marked sections of the Technical Proposal. Refer to Section L of the RFP for specific requirements. Read each section below carefully. In some cases, offerors may be asked to provide documentation which is in addition to the minimum requirements identified in Section L.

1) Obtaining and Disseminating Biomedical Research Resources

Section L of the RFP specifies the minimum documentation requirements for this element. The Technical Proposal should document all information necessary to evaluate this issue.

2) Sharing Research Data (Plan)

Section L of the RFP specifies the minimum documentation requirements for Data Sharing. All related documentation should be included in the proposal in this clearly marked section. The Technical Proposal should include a plan for Data Sharing as required by this RFP.

3) Information Technology (IT) Systems Security

Section L of the RFP specifies the minimum documentation requirements for IT Systems security. All related documentation should be included in the Technical Proposal in this clearly marked section. The Technical Proposal should include a plan for IT Systems security as required by this RFP.

ATTACHMENT 4: ADDITIONAL TECHNICAL PROPOSAL INSTRUCTIONS

ADDENDUM 1

Case Study 1: Feasibility Assessment of ITN Concept Proposal - Cytokine Production in Children with Pre-Clinical and Clinical Type 1 Insulin Dependent Diabetes Mellitus

Instructions to Offerors: Perform a statistical feasibility assessment of the following Case Study: ITN Concept Proposal 123123. In preparing your assessment, please provide a single document with your critical analysis of the following Concept Proposal for this case study not to exceed 10 single-spaced pages in length:

1. Assessments of the proposed vs. one or more preferred study design options for this observational trial. The weaknesses in the Concept Proposal that follows are intentional to allow considerable "room for improvement" in your critical evaluation.

2. Assessments of the proposed vs. one or more preferred study objective(s) for this trial. Please include a final set of recommendations as to how best to revise the entire document for improved clarity.

3. Assessments of the proposed inclusion and exclusion criteria for pre-diabetic participants, controls, and new-onset diabetics. Address ways to provide added clarity to the process of "matching control participants" to the pre-diabetic and to the new-onset diabetic participants in this study and a final set of recommendations as to how best to revise the entire document for improved clarity.

4. Assessments of the proposed vs. one or more preferred sample size estimates and justification, with a clear list of all assumptions used in creating your analysis.

5. Assessments of the proposed vs. a preferred accrual period and completion period for this trial with clear explanation for your rationale.

6. Assessments of the proposed vs. preferred blinding methods for this trial.

7. Evaluations of the selected vs. preferred endpoints for this trial.

8. Evaluation of the proposed vs. an improved statistical and data analysis plan for this trial. Address directly potential ways to compare the various cohorts in this study statistically for a single cytokine labeled as "Interleukin – X".

Note: If any critical information has been omitted from this case study, please make an explicitly stated reasonable assumption in order to complete the feasibility assessment.

Case Study Synopsis

Title	Cytokine Production in Children with Pre-Clinical and Clinical Type I Insulin Dependent Diabetes Mellitus
Short Title	Cytokine production in diabetic and pre-diabetic children
Sponsor	NIAID and the Immune Tolerance Network
Concept Proposal Number	ITN123123
Principal Investigator	John Doe, MD
Participating Site(s)	University of XYZ.
Accrual Objective	A total approximately 380 children will be enrolled in this study
Accrual Period	3 years
Study Design	This is an observational study with no intervention. **Group 1**: Pre-Diabetic Participants: 60 children with two defined autoantibodies (IAA, GADA or IA-2A) **Groups 2-5**: Controls (60 per group X 4 groups = 240) age-, sex- and HLA-matched children negative for the three autoantibodies listed above. P Group 2: Control Participant #s 01-60 P Group 3: Control Participant #s 61-120 P Group 4: Control Participant #s 121-180 P Group 5: Control Participant #s 181-240 **Group 6**: Recent onset IDDM: 80 children with newly diagnosed IDDM
Sample Size	Target = 380 participants. Note: Only minimum accrual objectives have been established for each group. When possible and feasible, attempts will be made to surpass such goals.
Study Duration	Up to 3 years
Primary Study Objective	The overall objective of this study is to define immunological markers and establish assays capable of predicting beta-cell destruction and clinical onset of IDDM.

Eligibility Criteria	Pre-Diabetic Participants • enrolled in the parent study "Diabetes Prediction and Prevention Program (DIPP)" • positive for two of the following autoantibodies; IAA, GADA or IA-2A • seroconversion to autoantibody positivity occurred ≥ one year and ≤ five years prior to enrollment • patient or parent willing to provide informed consent Controls • enrolled in the parent study "Diabetes Prediction and Prevention Program (DIPP)" • negative for diabetes-associated autoantibodies • age, sex and HLA-matched with autoantibody-positive participant New-Onset Diabetics • participant has IDDM • participant was diagnosed 2-7 days prior to enrollment
Exclusion Criteria	• Autoimmune disease, other than IDDM
Summary of Study Procedures	Eligible participants who meet the criteria for their respective study group and who provide informed consent will be enrolled. Participants will sign a multi-option informed consent. All participants will consent to the collection of demographic information, medical history, and clinical information. Participants will consent to the collection of blood every three months (pre-diabetics), twelve months (controls) or one time only (early-onset diabetics) to be used for immune tolerance assays. (See Appendix 1 and 2 for details.)
Tolerance Assay Studies	Peripheral Blood Gene Expression-Gene Chips/RT PCR Frozen PBMC-ELISPOT Flow Cytometry-Panel Staining PBMC Intracellular Cytokines, Insulin autoAB Tetramer Autoantibody

Background and Scientific Rationale

Insulin Dependent Diabetes Mellitus (IDDM) is an immune-mediated disease in which pancreatic beta cells are destroyed in a process usually lasting for a prolonged period, often several years or even decades. Prediction of disease development is possible during the long prediabetic period using established markers such as various diabetes-associated autoantibodies targeting several autoantigens in pancreatic islet

cells. These autoantibodies have been traditionally measured using immunofluorescence and microscopy to detect islet cell antibodies (ICA). These include insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GADA) and the IA-2 antibodies (IA-2A).

Markers are needed that allow a better characterization of the ongoing immune response in order to predict whether the process of beta-cell damage is ongoing and, in intervention trials, to monitor the effect of experimental treatments. Included among current autoantibody marker profiles associated with higher risk for progression to overt diabetes are positivity for multiple autoantibodies and the presence of IA-2 antibodies. The problem with these markers is that they emerge in the late phase of the autoimmune process when it may be too late to intervene. A lot of attention has been paid to the measurement of T-cell function because of their central role in the effector mechanisms determining beta cell destruction. However, T-cell assays specific for diabetes-associated autoantigens have turned out to be difficult to standardize and are characterized by poor reproducibility. In addition, considerable overlapping has been observed in antigen-specific T-cell responses between patients with IDDM and unaffected control subjects. These difficulties derive at least partly from the problems associated with the production of well purified, immunologically active antigen preparations.

The proposed study is based on the study population and sample material produced by the Diabetes Prediction and Prevention (DIPP) project run at the JDRF Center for Prevention of Type 1 Diabetes. The extensive follow-up protocol includes blood sampling, beginning at birth, at 3-6 month intervals in children at genetic risk for IDDM. This allows characterization of early events in the autoimmune response and evaluation of the correlation between these markers and later outcome of the children.

Insulin autoantibodies appear often as the first autoantibody in children who develop islet-cell autoimmunity. Recent studies indicate that primary immunization to insulin is induced in early infancy by exposure to dietary bovine insulin present in cows' milk formulas and may be an explanation for the association between short breast feeding, early introduction of cows' milk-based formula and increased risk of IDDM. Insulin-specific T cells have also been associated with diabetes-related autoimmunity in man and in a mouse model where a majority of the islet-infiltrating lymphocytes have been shown to be specific for insulin.

Insulin-specific immunity alone is clearly non-specific for IDDM and antigenic spreading may be of central importance. Results from the DIPP study suggest that IAA are characterized by high sensitivity, early appearance, and high frequency of transient antibody positivity, whereas ICA detected with a standardized assay appear to be more specific for the screening of beta-cell autoimmunity in young children with increased genetic susceptibility to IDDM. Thus, this study will examine autoantibody development of insulin autoantibody and another major autoantigen, GAD65.

OBJECTIVES

The overall objective of this study is to define immunological markers and establish assays capable of predicting beta-cell destruction and clinical onset of IDDM.

These assays will be designed to:

1. detect ongoing (auto)immune processes reflected by activating circulating cells and their increased production of cytokines promoting tissue destruction or the decreased synthesis of cytokines promoting suppression.
2. detect specific sensitization to target autoantigens and the presence of destructive effector T cell clones.

Study Design and Population

Statement of Goals

The goal of this study is to establish assays capable of detecting the initiation of islet cell-specific immunity, the destructive capacity of this response and its natural development towards the clinical onset of IDDM.

Specifically,

- To detect ongoing autoimmune processes reflected by activated circulating cells and their increased production of cytokines promoting tissue destruction, or decreased production of cytokines promoting suppression.
- To detect specific sensitization to target autoantigens and the presence of destructive effector T cell clones.

Description of Study Design and Control Methods

This is an observational study with no intervention. This study will involve children previously enrolled in the Diabetes Prediction and Prevention (DIPP) project run at the JDRF Center for Prevention of Type 1 Diabetes.

Approximately 380 pre-diabetics, controls and early onset diabetics will be recruited into the study. The recruitment period for this study will be for 3 years after the first participant is enrolled. Participants will be classified into the following groups:

- Group 1: Pre-diabetic group - 60 children with autoantibodies to at least two of the following biochemically defined antigens; insulin, GAD, IA-2.
- Groups 2-5: Control groups – 240 age-, sex- and HLA-matched children negative for the three autoantibodies listed above.

  Group 2: Control Participant #s 01-60

  Group 3: Control Participant #s 61-120

  Group 4: Control Participant #s 121-180

  Group 5: Control Participant #s 181-240
- Group 6: Recent onset IDDM - 80 children with newly diagnosed IDDM. These children are randomized for a treatment protocol with intranasal insulin or placebo. For the purposes of this trial, treatment with intranasal insulin (or placebo) will be collected as a concomitant medication.

Pre-Diabetic and control participants will be followed for three years.

Study Population, Sample Times, Volume Amounts, and Assays to be Performed

Blood will be obtained at baseline following receipt of informed consent, eligibility verification and group assignment.

Additional clinical and demographic data will also be collected at baseline. Information on concomitant medications, including status in intranasal insulin study for diabetic participants, will be recorded.

Pre-diabetic participants will return every three months and control participants will return every 12 months for additional blood draws. Blood will be used for immune tolerance studies according to the tables in Appendices 1 and 2.
Diabetic participants will be drawn one time only.

Screening and Enrollment
This research study will be explained in lay language to each potential research participant. The participant will sign an informed consent prior to any screening study procedures. Participants who are deemed qualified for the study will be enrolled and assigned a unique participant identification number (PID).

Selection and Withdrawal of Participants

Inclusion Criteria

Pre-Diabetic Participants

1. enrolled in Diabetes Prediction and Prevention Program (DIPP)
2. positive for two of the following autoantibodies; IAA, GADA, IA-2A
3. seroconversion to autoantibody positivity occurred ≥ one year and ≤ five years prior to enrollment, the data of seroconversion will be defined as the date of first appearance of one or more autoantibodies
4. patient or parent willing to provide informed consent

Controls

1. enrolled in Diabetes Prediction and Prevention Program (DIPP)
2. age ≥ 3 years
3. negative for diabetes-associated autoantibodies
4. age, sex and HLA-matched with autoantibody-positive participant meeting inclusion criteria in Section 4.1.1
5. preferably drawn on same day as participant in Section 4.1.1

New-Onset Diabetics

1. participant has IDDM
2. participant was diagnosed 2-7 days prior to enrollment

Exclusion Criteria

1. autoimmune disease, other than IDDM

Participant Withdrawal Criteria

Premature Termination from the Study

Study participants may terminate from the study at any time by their own choice or at the discretion of the principal investigator.

Statistical Considerations and Analytical Plan

Study Objectives

The objectives of this study are

- To detect ongoing autoimmune processes reflected by activated circulating cells and their increased production of cytokines promoting tissue destruction, or decreased production of cytokines promoting suppression.
- To detect specific sensitization to target autoantigens and the presence of destructive effector T cell clones.

Sample Size and Statistical Power

Given the lack of precedent mechanistic studies investigating sizable groups of early-onset diabetic participants, pre-diabetic participants and HLA-matched controls with concomitant identification of markers of the tolerant state, the sample sizes, both for the study overall and the individual groups, are largely empirical and based upon clinical judgment of reasonable, achievable accrual objectives. However, it will be noted that only minimum accrual objectives have been established for each group, implying that, when possible and feasible, attempts will be made to surpass such goals. Depending on the specific nature of the statistical analysis methodologies used, it may be possible to implement post hoc analyses of the power achieved by the study. Such analyses which result from this pilot study may allow for the proper calculation of effect size for use in the planning of future mechanistic studies of a similar nature.

Blinding

Participants who are deemed qualified for the study will be enrolled and assigned a unique participant identification number. All activities performed in conjunction with this study will be performed in an unblinded manner.

Statistical Analyses

Analysis Samples

Participants who are deemed qualified for the study will be enrolled and will comprise the analysis population. The demographic, clinical, laboratory, and assay data collected for these participants will comprise the analysis database, except in those cases in which the participant has terminated from the study prior to the donation of biologic specimens.

Description of Baseline Characteristics and Demographics

Demographic and baseline characteristic data will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum for continuous variables; counts and percents for categorical variables).

Use of Medications

All medication use will be coded using the World Health Organization (WHO) drug dictionary. The number and percentage of participants receiving prior and concomitant immunosuppressive medications/therapies will be presented overall and by medication class.

Study Completion

The percent of participants who fail to complete the study, losses to follow-up, times to loss to follow-up, and reasons for discontinuation (adverse events, other) will be presented for each study group.

Analysis of Assay Data

Statistical methodologies and analyses will be utilized for evaluation of all aspects of the assay data, including examination of correlation with functional tolerance and the elucidation of responsible mechanisms.

No imputations will be made to account for missing data. No adjustments will be made to account for variation between the centers, although summaries may be broken down by center. All statistical tests will be two-sided with $\alpha=0.05$ and will be used to determine if mean changes within a study group are statistically significantly different than zero.

Assay summaries will be based on raw values, change from baseline values, and percent change from baseline values. Measurements will be summarized with descriptive statistics at each visit for each study group. Inferential analyses of the change from baseline will test the null hypothesis that the change is equal to zero versus the alternate hypothesis that the change is not equal to zero. If the changes are reasonably close to being normally distributed, then paired t-tests will be used to perform these tests. Otherwise, Wilcoxon signed-rank tests will be used.

Safety

All participants enrolled in the study will be included in all safety analyses. Safety parameters to be displayed for each Study Group will include adverse events as defined for this assay study. Adverse events will be classified using the NCI-CTC grading scale and coded using the MedDRA dictionary. The number and incidence of adverse events by body system and preferred term will be summarized. Adverse events by maximum severity will be assessed by Study Group. Separate summaries will be provided for serious adverse events as well as adverse events leading to study discontinuation.

APPENDIX 1

Assays Schedule for Pre-Diabetic and Control Subjects													
						Months							
Study Visit	**SCR 00**	**BSL 0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**
Visit Numbers	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
General Assessments													
Initial patient contact	X												
Inclusion/Exclusion Criteria, Informed Consent	X												
Medical records release form	X												
Medical and clinical history	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographic information	X												
Laboratory Assessments													
CBC (including differential, hemoglobin, hematocrit, and platelet)		X											
Metabolic profile (serum sodium, potassium, chloride, bicarbonate, BUN, creatinine and glucose)		X											
Tolerance Assay Studies													
Peripheral Blood Gene Expression-Gene Chips/RT PCR		X[1]				X[1]				X[1]			
Frozen PBMC-ELISPOT			X[2]				X[2]				X[2]		
Flow Cytometry-Panel Staining				X[3]				X[3]				X[3]	
PBMC Intracellular Cytokines, Insulin autoAB				X[3]				X[3]				X[3]	
Tetramer					X[4]				X[4]				X[4]
Autoantibody				X[3]				X[3]				X[3]	

[1] Control Participant #s 01-60
[2] Control Participant #s 61-120
[3] Control Participant #s 121-180
[4] Control Participant #s 181-240

Clinical Samples to be collected for Tolerance Assay Studies are as follows:

- RNA/RT-PCR – 6 ml
- ELISPOT – 10 X 10^6 frozen PBMC
- PBMC / Antigen-specific stimulation – 5-10 ml
- Autoantibody – 0.5 ml plasma
- Tetramer - 10 X 10^6 frozen PBMC

APPENDIX 2

Assay Schedule for Early-Onset Diabetic Subjects		
Study Visit	**SCR 00**	**BSL 0**
Visit Numbers	**-1**	**0**
General Assessments		
Initial patient contact	**X**	
Inclusion/Exclusion Criteria, Informed Consent	**X**	
Medical records release form	**X**	
Medical and clinical history	**X**	**X**
Demographic information	**X**	
CBC (including differential, hemoglobin, hematocrit, and platelet)		**X**
Metabolic profile (serum sodium, potassium, chloride, bicarbonate, BUN, creatinine and glucose)		**X**
Tolerance Assay Studies		
Peripheral Blood Gene Expression-Gene Chips/RT PCR		**X[1]**
Frozen PBMC-ELISPOT		**X[2]**
PBMC Intracellular Cytokines, Insulin autoAB		**X[3]**
Tetramer		**X[4]**
Autoantibody		**X[3]**
Laboratory Assessments		

[1] Diabetic Participant #s 01-20

[2] Diabetic Participant #s 21-40

[3] Diabetic Participant #s 41-60

[4] Diabetic Participant #s 61-80

ATTACHMENT 4: ADDITIONAL TECHNICAL PROPOSAL INSTRUCTIONS

ADDENDUM 2

Case Study 2: Feasibility Assessment of AADCRC Concept Proposal – Immune Responses to Natural Rhinovirus Infections in Individuals with Allergic Asthma, Allergic Rhinitis and Controls

Instructions to Offerors: Perform a statistical feasibility assessment of the following Case Study: AADCRC Concept Proposal 456456. In preparing your assessment, please provide a single document with your critical analysis of the following topics for this case study not to exceed 10 single-spaced pages in length. Weaknesses in the current plan have been included intentionally to allow "room for improvement."

9. Study design. Discuss the proposed vs. another preferred study design option for this research study.

10. Study objectives. Provide assessment of the proposed vs. other preferred and feasible study objective(s). Include a discussion of the main study objectives in relation to the descriptions given in Sections 2 and 3 with a set of recommendations as to how best to revise the entire document for improved clarity.

11. Inclusion and exclusion criteria for study subjects. Provide recommendations with justification for additional criteria or for removal of proposed criteria.

12. Study accrual and completion period. Provide recommendations for changes in the proposed accrual period and completion period for this study with justification.

13. Primary outcomes. Discuss the proposed primary outcomes and provide suggestions with justification for other outcomes that may better serve the objectives of this study.

14. Sample size estimates. Provide sample size analysis with justification, using assumptions for any information that is not offered. List all assumptions used in creating your assessment. Use the "considerations" that have been provided.

15. Statistical and data analysis. Provide a plan for this study.

Note: If any critical information from this case study has been omitted, please make an explicitly stated reasonable assumption in order to complete the feasibility assessment.

Case Study Synopsis

Title	Immune Responses to Natural Rhinovirus Infections in Individuals with Allergic Asthma, Allergic Rhinitis and Controls
Short Title	Immune Responses to Rhinovirus
Sponsor	NIAID
Concept Proposal Number	AADCRC456456
Principal Investigator	John Smith, MD
Participating Site(s)	University of ABC
Accrual Objective	A total of 450 children and adults will be enrolled in this study
Accrual Period	3 years
Study Design	One-year observational, mechanistic, single-center study of naturally occurring upper respiratory viral infections in children and adults.
Study Duration	Up to 4 years
Primary Study Objectives	A) To test the hypothesis that baseline interferon production by nasal airway epithelial cells and peripheral blood mononuclear cells, in response to rhinovirus infection, relates to the severity of naturally-occurring, rhinovirus-induced upper respiratory infections. B) To test the hypothesis that production of Type I, II and III interferons by nasal airway epithelial cells and peripheral blood mononuclear cells, in response to rhinovirus infection, are suppressed in individuals with allergic asthma, compared to those with allergic rhinitis alone and to non-asthmatic, non-rhinitic controls. C) To examine whether adults with asthma exhibit different interferon responses to natural rhinovirus infections and to *ex vivo* rhinovirus infection of nasal airway epithelial cells and peripheral blood mononuclear cells, compared to children with asthma.

Eligibility Criteria	• Gender: female and male • Age: Adults: ≥ 18 years, Children: ≥ 6 years • Allergic Asthma: a) history of mild to moderate persistent asthma since childhood; b) history of intermittent or persistent symptoms of rhinitis with reproducible seasonal pattern for at least 2 consecutive years; c) airways hyperresponsiveness; d) evidence of immediate hypersensitivity to aeroallergens to which the clinical presentation can be attributable • Allergic Rhinitis: a) history of intermittent or persistent symptoms of rhinitis with reproducible seasonal pattern for at least 2 consecutive years; b) no history of asthma or wheezing; c) no evidence of airways hyperresponsiveness; d) evidence of immediate hypersensitivity to aeroallergens to which the clinical presentation can be attributable • Control: a) no history of symptoms of rhinitis with reproducible seasonal pattern; b) no history of asthma or wheezing; c) no evidence of airways hyperresponsiveness; d) no evidence of immediate hypersensitivity to aeroallergens
Exclusion Criteria	A) Any other chronic illness requiring chronic treatment which may interfere with clinical and/or immune responses to viral infections B) Severe persistent or uncontrolled asthma C) Current use of allergen immunotherapy
Summary of Study Procedures	Eligible participants who provide informed consent and meet the screening criteria for their respective study group will be enrolled. Screening procedures include: clinical evaluation, lung function testing and testing for airways hyperresponsiveness, allergy skin testing or *in vitro* serum allergen-specific IgE determination. At study entry: phlebotomy, nasal lavage and nasal scraping. At 12 months: lung function testing, phlebotomy, nasal lavage and nasal scraping. During an upper respiratory symptom exacerbation (at least 1 event per subject): clinical evaluation of severity of the exacerbation, lung function testing, phlebotomy, nasal lavage and nasal scraping.

Background and Scientific Rationale

Asthma affects 7-8% of the US population and is more common in children than adults. Asthma is the most common cause of hospitalizations in the pediatric population. Most cases of asthma hospitalization and asthma death or near-death, are preceded by a period of disease exacerbation of variable length. In the majority of asthma exacerbations leading to hospitalization, viral respiratory infections have been identified, both in children and adults. Furthermore, respiratory viral infections

have been associated with the onset of asthma symptoms in young children. Rhinoviruses are the most common viruses linked to asthma exacerbations.

Atopy (IgE-mediated allergy) is present in 80% or more of children with asthma and in approximately 60% of adults with asthma, primarily those adults whose asthma began during childhood. Atopic individuals are generally allergic to multiple aeroallergens that are encountered both in the indoor and the outdoor environment. Identification of atopy to a particular allergen can be made either through *in vivo* skin testing or through *in vitro* measurement of allergen-specific IgE antibodies in the serum. Although most individuals with asthma are atopic, the majority of atopic individuals do not have asthma, but only exhibit upper airway disease in the form of allergic rhinitis. On the other hand, in their vast majority, people with asthma and atopy have allergic rhinitis. The reasons why some individuals develop allergic rhinitis and asthma whereas others develop allergic rhinitis alone are not understood.

Recently, a number of investigators have observed that the concomitant presence of atopy and of a viral infection constitutes a stronger risk factor for asthma exacerbations and hospitalizations than either atopy or viral infection alone. This raises the possibility that the presence of atopy alters immune responses to viral infections.

Investigators have begun examining immune responses to respiratory viral infections in individuals with asthma. Available information suggests that airway epithelial cells, alveolar macrophages and peripheral blood mononuclear cells have defective innate immune responses to rhinovirus infection characterized by reduced production of Type I, II and III interferons, molecules with pivotal antiviral activity.

A major question is whether the identified abnormalities in interferon production are related to the severity of viral infections. In addition, it is not known whether a) reduced interferon responses to rhinovirus are associated with atopic status or with the clinical phenotype of asthma and b) whether interferon responses to rhinovirus infection differ between children and adults with asthma. If atopy is the major factor associated with impaired interferon responses, it should be identified as a primary target for therapeutic interventions to reduce the viral infection burden on patients with asthma. Also, if differences between adults and children are to be identified, they can lead to age-specific immunologic investigations of the causes of the reduced interferon response.

Objectives

1. To test the hypothesis that baseline interferon production by nasal airway epithelial cells and peripheral blood mononuclear cells in response to *ex vivo* rhinovirus infection relates to the severity of naturally-occurring rhinovirus-induced upper respiratory infections.
2. To test the hypothesis that interferon production by nasal airway epithelial cells and peripheral blood mononuclear cells, in response to *ex vivo* rhinovirus infection is suppressed in individuals with allergic asthma, compared to those with allergic rhinitis alone and to non-asthmatic, non-rhinitic controls.
3. To examine whether adults with asthma exhibit different interferon responses to natural rhinovirus infections and to *ex vivo* rhinovirus infection of nasal airway epithelial cells and peripheral blood mononuclear cells, compared to children with asthma.

Study Design and Population

Statement of Goals

The goal of this study is to establish a human subject 6-group cohort (children with allergic asthma, adults with allergic asthma, children with allergic rhinitis, adults within allergic rhinitis, control children, control adults) that will be prospectively followed for 12 months and will be evaluated at regular time intervals and during exacerbations of upper airway symptoms.

Description of Study Design

SCREENING. Subjects will undergo screening evaluations at study entry. These will include a) clinical assessment with standardized questionnaires, b) physical examination, c) skin testing or phlebotomy for serum specific IgE determinations, d) lung function testing, e) bronchial provocation with methacholine.

BASELINE EVALUATIONS. Subjects who meet inclusion/exclusion criteria will undergo a) phlebotomy, b) nasal lavage and c) nasal scraping. The purpose of these procedures is to obtain material that will allow i) determination of viral infection status and ii) nasal airway epithelial and peripheral blood mononuclear cell production and expression of Type I, II and III interferons upon *ex vivo* exposure to rhinovirus.

FINAL EVALUATIONS (after 12 months of study participation). Subjects will undergo a) phlebotomy, b) nasal lavage and c) nasal scraping. The purpose of these procedures is to obtain material that will allow i) determination of viral infection status and ii) nasal airway epithelial and peripheral blood mononuclear cell production and expression of Type I, II and III interferons upon *ex vivo* exposure to rhinovirus.

INTERIM EVALUATIONS. Subjects will be instructed to contact the study personnel upon development of increased upper respiratory symptoms for 24 hours. They will be either asked to visit the study center or a home visit will be scheduled within 48 hours by the study personnel. During this study visit, they will have a clinical assessment of their respiratory condition, current medications will be recorded and they will undergo a) lung function testing (portable spirometry), b) phlebotomy, c) nasal lavage and d) nasal scraping. Finally, they will be asked to record and score daily upper and lower airway symptoms for the next 2 weeks.

INTERIM PHONE EVALUATIONS. Every 2 months, subjects will be contacted by a member of the study staff and will be asked to respond to a clinical questionnaire regarding the level of activity of their respiratory condition. The purpose of this information is to support subject retention and to identify any events that may jeopardize subjects' continuing participation in the study. Changes in medications will also be recorded.

Study Population, Procedures and Assays to be Performed

STUDY POPULATION

I. Children with allergic asthma, N=75
II. Adults with allergic asthma, N=75
III. Children with allergic rhinitis, N=75
IV. Adults with allergic rhinitis, N=75
V. Control children, N=75
VI. Control adults, N=75

PROCEDURES

I. Screening Questionnaires (diagnostic and safety purpose)
II. Physical Examination (safety purpose)
III. Allergy skin testing (to determine atopic status)
IV. Phlebotomy (to measure serum allergen specific IgE and/or to obtain peripheral blood mononuclear cells)
V. Spirometry (lung function testing)
VI. Methacholin bronchoprovocation (to test for airways hyperresponsiveness)
VII. Nasal lavage (to obtain secretions for viral identification)
VIII. Nasal scraping (to obtain nasal airway epithelial cells)
IX. Isolation and rhinovirus infection of peripheral blood mononuclear cells
X. Culture and rhinovirus infection of nasal airway epithelial cells
XI. Symptom diary for both upper and lower airways symptoms (to determine the severity and duration of a clinical exacerbation)

ASSAYS

I. Serum allergen specific IgE determination (CAP tests)
II. Measurement of interferons α, β, γ and λ in supernatants of peripheral blood mononuclear cells and nasal airway epithelial cells using ELISA or Luminex techniques
III. Quantitative RT-PCR on RNA isolated from peripheral blood mononuclear cells and nasal airway epithelial cells
IV. Quantitative PCR in nasal secretions for detection of respiratory viruses
V. Culture and rhinovirus infection of nasal airway epithelial cells and peripheral blood mononuclear cells

Selection and Withdrawal of Participants

Inclusion Criteria

ALLERGIC ASTHMA PARTICIPANTS

I. Gender: female and male
II. Age: Adults: $\geq$ 18 years, Children: $\geq$ 6 years
III. History of mild to moderate persistent asthma since childhood
IV. History of intermittent or persistent symptoms of rhinitis with reproducible seasonal pattern for at least 2 consecutive years
V. Airways hyperresponsiveness: methacholine PC_{20} < 8 mg/ml
VI. Evidence of immediate hypersensitivity to aeroallergens to which the clinical presentation can be attributable

ALLERGIC RHINITIS PARTICIPANTS

I. Gender: female and male
II. Age: Adults: ≥ 18 years, Children: ≥ 6 years
III. History of intermittent or persistent symptoms of rhinitis with reproducible seasonal pattern for at least 2 consecutive years
IV. No history of asthma or wheezing
V. No evidence of airways hyperresponsiveness: methacholine PC_{20} > 25 mg/ml
VI. Evidence of immediate hypersensitivity to aeroallergens to which the clinical presentation can be attributable

CONTROLS

I. Gender: female and male
II. Age: Adults: ≥ 18 years, Children: ≥ 6 years
III. No history of symptoms of rhinitis with reproducible seasonal pattern
IV. No history of asthma or wheezing
V. No evidence of airways hyperresponsiveness: methacholine PC_{20} > 25 mg/ml
VI. No evidence of immediate hypersensitivity to aeroallergens

EXCLUSION CRITERIA

I. Any other chronic illness requiring treatment which may interfere with clinical and/or immune responses to viral infections
II. Severe persistent or uncontrolled asthma
III. Current use of allergen immunotherapy

Participant Withdrawal Criteria

Study participants may terminate the study at any time by their own choice or at the discretion of the principal investigator.

Statistical Considerations and Analytical Plan

Study Objectives and Outcomes

OBJECTIVES

1. To test the hypothesis that baseline interferon production by nasal airway epithelial cells and peripheral blood mononuclear cells in response to ex vivo rhinovirus infection relates to the severity of naturally-occurring, rhinovirus-induced, upper respiratory infections.

PRIMARY OUTCOMES

I. Study entry interferon α, β, γ and λ levels in supernatants of peripheral blood mononuclear cells and nasal airway epithelial cells
II. Combined upper and lower airways symptom scores averaged over 14 days from the diaries obtained during a naturally-occurring, rhinovirus-induced, upper respiratory infection

SECONDARY OUTCOMES

I. FEV_1, FVC and FEV_1/FVC changes from baseline at the evaluation that will take place during a naturally-occurring, rhinovirus-induced, upper respiratory infection
II. Study entry quantitative RT-PCR outcomes for interferon α, β, γ and λ messenger RNA in peripheral blood mononuclear cells and nasal airway epithelial cells
III. Interferon α, β, γ and λ levels in supernatants of peripheral blood mononuclear cells and nasal airway epithelial cells obtained during a naturally-occurring, rhinovirus-induced, upper respiratory infection
IV. Quantitative RT-PCR outcomes for interferon α, β, γ and λ messenger RNA in peripheral blood mononuclear cells and nasal airway epithelial cells obtained during a naturally-occurring, rhinovirus-induced, upper respiratory infection
V. Upper airways symptom scores averaged over 14 days from the diaries obtained during a naturally-occurring, rhinovirus-induced, upper respiratory infection
VI. Lower airways symptom scores averaged over 14 days from the diaries obtained during a naturally-occurring, rhinovirus-induced, upper respiratory infection

2. To test the hypothesis that interferon production by nasal airway epithelial cells and peripheral blood mononuclear cells in response to ex vivo rhinovirus infection is suppressed in individuals with allergic asthma, compared to those with allergic rhinitis alone and to non-asthmatic, non-rhinitic controls.

PRIMARY OUTCOMES
I. Study entry interferon α, β, γ and λ levels in supernatants of peripheral blood mononuclear cells and nasal airway epithelial cells

SECONDARY OUTCOMES
I. Study entry quantitative RT-PCR outcomes for interferon α, β, γ and λ messenger RNA in peripheral blood mononuclear cells and nasal airway epithelial cells
II. Interferon α, β, γ and λ levels in supernatants of peripheral blood mononuclear cells and nasal airway epithelial cells obtained during a naturally-occurring, rhinovirus-induced, upper respiratory infection
III. Quantitative RT-PCR outcomes for interferon α, β, γ and λ messenger RNA in peripheral blood mononuclear cells and nasal airway epithelial cells during a naturally-occurring, rhinovirus-induced, upper respiratory infection

3. To examine whether adults with asthma exhibit different interferon responses to natural rhinovirus infections and to ex vivo rhinovirus infection of nasal airway epithelial cells and peripheral blood mononuclear cells, compared to children with asthma.

PRIMARY OUTCOMES
I. Study entry interferon α, β, γ and λ levels in supernatants of peripheral blood mononuclear cells and nasal airway epithelial cells
II. Interferon α, β, γ and λ levels in supernatants of peripheral blood mononuclear cells and nasal airway epithelial cells obtained during a naturally-occurring, rhinovirus-induced, upper respiratory infection

SECONDARY OUTCOMES

I. Study entry quantitative RT-PCR outcomes for interferon α, β, γ and λ messenger RNA in peripheral blood mononuclear cells and nasal airway epithelial cells
II. Quantitative RT-PCR outcomes for interferon α, β, γ and λ messenger RNA in peripheral blood mononuclear cells and nasal airway epithelial cells during a naturally-occurring, rhinovirus-induced, upper respiratory infection

Sample Size and Statistical Power

CONSIDERATIONS

I. It is estimated that approximately 10 subjects per group will drop out of the study for various reasons
II. It is estimated that another 15 subjects per group will not suffer from a rhinovirus-induced upper respiratory infection in the course of the 12 months of the study or that they will fail to notify the study staff when they are experiencing a symptom exacerbation that may qualify as a rhinovirus-induced upper respiratory infection
III. It is estimated that 30 subjects in each group will experience (and will be evaluated for) more than 1 rhinovirus-induced upper respiratory infection during the course of the study
IV. In previously published work, bronchial epithelial cells from individuals with asthma, when exposed to rhinovirus16 ex vivo, produced 900$\pm$450 (x$\pm$SD) pg/ml of interferon λ in their supernatants. Epithelial cells obtained from healthy individuals and treated under the same conditions produced 1700$\pm$1200 (x$\pm$SD) pg/ml of interferon λ.

Statistical Analyses

ANALYSIS SAMPLES

Participants who are deemed qualified for the study will be enrolled and will comprise the analysis population. The demographic, clinical, laboratory, and assay data collected for these participants will comprise the analysis database, except in those cases in which the participant has terminated from the study prior to the donation of biologic specimens.

DESCRIPTION OF BASELINE CHARACTERISTICS AND DEMOGRAPHICS

Demographic and baseline characteristic data will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum for continuous variables; counts and percents for categorical variables).

STUDY COMPLETION

The percent of participants who fail to complete the study, losses to follow-up, times to loss to follow-up, and reasons for discontinuation (adverse events, other) will be presented for each study group.

ANALYSIS OF ASSAY DATA

Statistical methodologies and analyses will be utilized for evaluation of all aspects of the assay data.

No imputations will be made to account for missing data. All statistical tests will be two-sided with $\alpha=0.05$.

Assay summaries will be based on raw values, change from baseline values, and percent change from baseline values. Measurements will be summarized with descriptive statistics at each visit for each study group. Inferential analyses of the change from baseline will test the null hypothesis that the change is equal to zero versus the alternate hypothesis that the change is not equal to zero. If the changes are reasonably close to being normally distributed, paired t-tests will be used. Otherwise, the analysis will be conducted using non-parametric statistics.

SAFETY

All participants enrolled in the study will be included in all safety analyses.

Adverse events will be classified using the NCI-CTC grading scale and coded using the MedDRA dictionary. The number and incidence of adverse events by body system and preferred term will be summarized. Separate summaries will be provided for serious adverse events as well as adverse events leading to study discontinuation.

ATTACHMENT 4: ADDITIONAL TECHNICAL PROPOSAL INSTRUCTIONS

ADDENDUM 3

Case Study 3: Feasibility Assessment of ITN Full Application –

Phase II Clinical Trial of Tolerance Induction for Active Rheumatoid Arthritis

Instructions to Offerors: Perform a statistical feasibility assessment of the following Case Study: ITN Full Application 0001AI. In preparing your assessment, please provide a single document with your critical analysis of this Full Application not to exceed 10 single-spaced pages in length; include the following topics in your feasibility assessment:

1. Assessments of the proposed vs. one or more preferred study design options for this interventional trial.

2. Assessments of the proposed vs. one or more preferred study objective(s) for this trial.

3. Assessments of the proposed vs. one or more preferred sample size estimates and justification, with a clear list of all assumptions used in creating your analysis.

4. Assessments of the proposed vs. a preferred accrual period and completion period for this trial with clear explanation for your rationale.

5. Assessments of the proposed vs. preferred blinding methods for this trial.

6. Evaluations of the selected vs. preferred primary endpoint(s) for this trial.

    a. Please evaluate the following scenario: NIAID receives feedback from an FDA pre-IND review of the full application study design that recommends a change in the selected time point for primary efficacy. "FDA recommends a six month endpoint is necessary to support drug development for the treatment of patients with RA. FDA guidance documents recommend continuous monitoring of safety and clinical response to therapy for no less than six months." (Please see the Synopsis for statistical assumptions.)

    b. Please revise the full application study design with recommendations for revised sample size and power calculation estimates to include evaluations of safety and clinical efficacy for drug 1, drug 2, and combination therapy with both drugs 1 and 2.

7. Evaluation of the proposed vs. an improved statistical and data analysis plan for this trial. Address directly potential ways to compare the various cohorts in this study statistically for a single cytokine labeled as "Interleukin – X". (This should be treated as an additional mechanistic endpoint for this study.) Please make final recommendations for ways to improve the statistical and data analysis plans for this study.

Note: If any critical information from this case study has been omitted, please make an explicitly stated reasonable assumption in order to complete the feasibility assessment.

Case Study 3 Synopsis

Title	Tolerance Induction with Drugs 1 and 2 in Participants with Active Rheumatoid Arthritis (RA).
Short Title	"Tolerance for Active RA".
Sponsor	NIAID and the Immune Tolerance Network
ITN Full	ITN0001AI
Application Number	
Principal Investigator	Jane Doe, MD
Participating Site(s)	2 sites (University of X and University of Y).
Primary Study Objective	This study aims to make a preliminary assessment of both clinical safety and clinical efficacy to determine whether the combined immunomodulatory properties of Drugs 1 and 2 can increase the proportion of RA participants achieving clinical remission compared to either drug alone.
Accrual Objective	A total of approximately **100** participants will be enrolled in this study **Group 1: 15** participants **Group 2a: 70** participants **Group 2b: 15** participants
Accrual Period	6 months
Study Design	A phase II, open label, single blinded clinical trial of participants with active rheumatoid arthritis (RA). **Group 1:** Once cycle of Drug 2 will be administered by daily i.v. infusion for up to 5 days . Thereafter, continue with methotrexate for the duration of the study (24 wks). **Group 2a:** Drug 1 will be administered at a dose of 3mg/kg by i.v. infusion at baseline, 2, 6 and then at 8 weekly intervals for the duration of the study. Participants achieving a DAS28 < 4.0 at 14 weeks will continue treatment with Drug 1 and methotrexate for the duration of the study. **Group 2b:** Participants failing to achieve this level of clinical response (DAS28 ≥ 4.0) will receive a fourth and final infusion of Drug 1. Within one week of this infusion participants will receive a single course of Drug 2 infusions, as described for Group 1, and thereafter continue with methotrexate monotherapy for the duration of the study.
Primary Efficacy Endpoints	1. The proportion of participants achieving an ACR50 clinical response at 4 weeks. 2. The proportion of participants achieving an ACR50 clinical response at 14 weeks.

Secondary Endpoints

1. The number of participants achieving clinical remission at 4 weeks (DAS28 <2.6).
2. The number of participants achieving clinical remission at 14 weeks (DAS28 <2.6).
3. Frequency of adverse events
4. Frequency of serious adverse events
5. Frequency of treatment-related adverse events of Grade 3 or higher severity

Study Duration

Up to 1 year

Study Hypotheses

Null Hypothesis: Pretreatment with Drug 1 provides no added benefit when combined with Drug 2.

Alternate Hypothesis: Pretreatment with Drug 1 does provide clinically significant benefit when combined with Drug 2.

Statistical Plan

This study aims to make a preliminary assessment of efficacy; it is NOT powered to make any formal comparisons between treatment groups because the efficacy of Drug 2 in patients with RA is not yet known.

Assumptions:

1. Therapy with Drug 1 in RA patients is generally beneficial in 60 – 70% of all patients. However, a significant minority of RA pts do not respond.

2. The investigators assume that ACR 50 responder rates to Drug 2 will be ~ 40% based on previous pilot study data.

3. Assuming a true ACR50 responder rate of at least 40%, there is a 91% chance of seeing at least 4 participants in a group of 15 participants with an ACR50 response at 14 weeks. With the same number of participants, a true response rate of only 20%, there would be an 83% probability of seeing at least 2 responders.

Inclusion Criteria

1. Age 18-70 years at screening
2. Diagnosis with early RA (defined as disease duration ≤ 3 years by the 1987 revised ACR criteria [Appendix 1])
3. Active RA disease in spite of therapy with methotrexate as evidenced by a high residual disease burden with DAS(ESR)28>5.1.
4. Patients are actively being treated with methotrexate and on a stable dose between 7.5mg and 25mg PO or SQ weekly for at least 8 weeks.
5. Prednisone (or equivalent corticosteroid) at stable dose of ≤ 10mg/day for 28 days.

Exclusion Criteria	1. The following laboratory parameters at the screening visit: a. Neutropenia (ANC < 1,500/uL) b. Thrombocytopenia (platelets < 100,000/uL) c. Anemia (Hgb <9 g/dL) d. Greater than or equal to 2 times the upper limit of normal for any of the following liver function tests: aspartate transaminase (AST), alanine transaminase (ALT), or alkaline phosphatase (ALP) e. Renal insufficiency (serum creatinine > 1.5 mg/dL) 2. Identified definitive diagnosis of another autoimmune disease, including but not limited to: SLE, scleroderma, primary Sjogren's syndrome, primary vasculitis, psoriasis, multiple sclerosis, anklyosing spondylitis, inflammatory bowel disease. 3. Intraarticular injections of corticosteroids within the 4 weeks prior to enrollment. 4. Concomitant use of DMARDs other than methotrexate (including but not limited to Hydroxychloroquine, Doxycycline, Minocycline, Leflunomide, Gold salts, Sulfasalazine, Cyclosporine) within 4 weeks of baseline. 5. Presence of open wounds or skin ulcers 6. Chronic or persistent infection that might be worsened by immunosuppressive treatment (including but not limited to human immunodeficiency virus [HIV], hepatitis B, hepatitis C, listeriosis, tuberculosis [TB], or significant opportunistic infection).

Background Information and Scientific Rationale

Background

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause characterized by persistent inflammatory synovitis. It is seen throughout the world and affects all races. This disease has a predilection for women in the 4th to 6th decades of life and targets synovial joints in a symmetric distribution. A genetic association between RA and specific HLA-DRB1 alleles, the characteristic patterns of lymphoid infiltrates in inflamed synovial joints, and the recent clinical benefits achieved with T-cell depletion therapies all point to a major role for T cells in the initiation and maintenance of the chronic inflammatory process. In a significant proportion of participants, the disease has a chronic course associated with rapidly progressive joint damage, chronic pain and

disability, and reduced quality of life associated with significantly increased mortality rates.

Since joint damage and impaired function may occur early in the natural history of the disease, health costs and loss of capacity to work impose significant economic burden on health systems around the world. There is thus an urgent need to define cost effective therapies that will completely suppress the inflammatory process.

It is generally agreed that combination therapy with Drug 1 and methotrexate constitutes "current best therapy" in RA. In spite of progress, there exist no tolerance-inducing drug regimens, since most efforts to target T cells by depletion or through the use of conventional immunosuppressive agents (e.g. cyclosporine A), have proved disappointing.

Furthermore, these regimens put already compromised participants at further risk of infections. For all of the reasons outlined above there is both an urgent need and a compelling rationale to combine current "best treatment" with agents that have the potential to induce sustained remission by inducing immunological tolerance. Such tolerising regimens should aim for periods of biologic-free remission, thereby significantly reducing long term exposure to potentially toxic agents.

The rationale for combining Drug 1 with Drug 2 therapy is compelling in many respects:

1. Both agents have been shown independently to have immunomodulatory properties in the clinical setting, leading to periods of drug or biologic free remission or clinical immune tolerance.
2. There is evidence from some but not all studies for a relative deficiency of Tregs in RA and both agents appear to enhance Treg function and/or numbers in participants.
3. Inflammation in general perturbs T cell antigen receptor (TCR) dependent signaling suggesting that active inflammation may attenuate tolerogenic signals induced by Drug 2. Thus, pre-treatment with Drug 1 might restore tolerogenic signals transduced by the TCR by drugs such as Drug 2.
4. Drug 2-induced cytokine release syndrome (CRS), which has substantially limited its use in the clinic, is modulated by Drug 1 as demonstrated in participants treated for acute allograft rejection as well as in mouse models.
5. Since no dominant RA autoantigen has been defined to date, Drug 2 offers one strategic approach for antigen specific immunotherapy. In summary, we propose that administration of Drug 1 creates an optimal systemic immunomodulatory milieu to facilitate tolerance induction with Drug 2.

Scientific Rationale for the Proposed Trial

Preclinical data indicate that Drugs 1 and 2 are superior to the use of either drug alone in a chronic relapsing model of collagen-induced arthritis, and preliminary unpublished data point to efficacy of Drug 2 alone in participants with RA.

This study will therefore explore whether the combined immunomodulatory properties of Drugs 1 and 2 can increase the proportion of RA participants achieving clinical remission compared to either drug alone through mechanisms relating to changes in the activity of regulatory T cells in vivo.

Thus, RA may perturb tolerogenic signals, and blocking inflammation with Drug 1 prior to treatment with Drug 2 should restore the integrity of TCR signal transduction pathways in effector T cells (leading to enhanced depletion) and regulatory T cells (leading to more robust immunomodulation).

Specifically, this study will address the impact of the chronic inflammatory response on tolerance induction in effector T cells with Drug 2, and how attenuation of inflammation with Drug 1 prior to tolerance induction could improve clinical efficacy as well as safety of Drug 2 in participants with active RA.

OBJECTIVE

The overall objective of this study is to test the combined safety and evaluate the preliminary efficacy of two biological agents (Drugs 1 and 2) in participants with RA. These two agents have previously been shown to have beneficial effects in other chronic inflammatory diseases. We propose to combine the anti-inflammatory and immunomodulatory properties of Drug 1 with the pro-tolerogenic effects of Drug 2 to test the hypothesis that Drug 1 plus Drug 2 therapy provides superior clinical benefit to either agent alone in a phase I/II open label, single blinded clinical trial of participants with active rheumatoid arthritis. The current study is designed to test the hypothesis that combination biologic therapy with Drugs 1 and 2 result in more favorable suppression of synovitis than either drug alone.

Study Design and Population

Description of Study Design and Control Methods

This study will involve a preliminary assessment of efficacy; it is not powered to make any formal comparisons between treatment groups because the efficacy of Drug 2 in patients with RA is not known.

The ACR50 response is used in defining the primary clinical efficacy endpoint as a standard clinical measure for many clinical trials performed since 1995 in participants with RA. ACR50 is defined as improvement of at least 50 percent in the number of both swollen and tender joints, as well as at least 50 percent improvement in three or more of the five remaining core set variables. In contrast to ACR20 responses, patients notice dramatic clinical differences following the achievement of ACR50 responses. The three major points supporting the use of disease activity measures (such as ACR50) in clinical trials of RA to try to achieve a goal of remission are the following:

1) Active RA leads to severe joint destruction, functional disability, and impaired health status;
2) Monitoring disease activity at regular, short-term intervals and appropriate modifications of disease modifying anti-rheumatic drugs (DMARD) therapy leads to significant functional and radiologic improvements; and,

3) Joint destruction frequently progresses even in states of low disease activity.

The primary clinical endpoints of this study will be the proportion of patients achieving an ACR50 response at 4 and 14 weeks. This is based on the assumption that ACR50 responder rates to Drug 2 will approximate to ~ 40%, which is within the range of responses seen at 14 weeks in patients with early RA after combination therapy with Drug 1 and methotrexate therapy (ACR50 ~ 60%). The investigators assume that therapy with Drug 1 in RA patients is generally beneficial in 60 – 70%. However, a significant minority of RA pts do not respond. Assuming a true ACR50 response rate of at least 40%, there is a 91% chance of seeing at least 4 patients in a group of 15 patients with an ACR50 response at 14 weeks. With the same number of patients, and a true response rate of only 20%, there would be an 83% probability of seeing at least 2 responders. Based on poor responder rates to Drug 1 a total of ~ 70 patients must be allocated to Group 1 (Drug 2) at study entry in order to recruit sufficient patients for Group 2b, who will receive Drug 2 after Drug 1.

Secondary endpoints will be the proportion of patients achieving clinical remission (DAS28 $\leq$ 2.6), and those achieving a EULAR moderate or good response at 4, 14 and 24 weeks. Exploratory endpoints will include the proportion of patients achieving sustained DAS28 $\leq$ 2.6 (remission) for more than 12 consecutive weeks once remission is achieved, the length of remission achieved according to DAS28 criteria, and time integrated DAS responses (AUC analysis). Other assessments will include time integrated CRP, the patient's self evaluation of functional status using the disability index of the Health Assessment Questionnaire (HAQ), Belza fatigue questionnaire, and the patient's self evaluation of quality of life using the Medical Outcomes Study Short Form 36 (SF-36). The effectiveness of patient recruitment and retention is supported by the record of the applicants' publications reporting results of completed studies. Compliance should be minimized by the in-patient stay and by the need for outpatient visits for administration of study drugs.

Analysis

The efficacy population will include all randomized patients and results will be presented according to randomized treatment group. The safety population will include all patients randomized who have at least one infusion of Drug 2 administered and results will be presented according to actual treatment group. Data will be reported descriptively, by treatment group. Patients who withdraw from the study will be included in the efficacy analyses as non-responders. A detailed statistical analysis plan will be drawn up and agreed with the investigators prior to study closure.

Appendix 1: ACR Criteria for Rheumatoid Arthritis

A. 1987 Revised American Rheumatism Association Criteria for Rheumatoid Arthritis

Four or more criteria must be present to diagnose rheumatoid arthritis.

1. Morning stiffness for at least one hour and present for at least six weeks.
2. Swelling of three or more joints for at least six weeks.
3. Swelling of wrist, metacarpophalangeal or proximal interphalangeal joints for six or more weeks.
4. Symmetric joint swelling for six or more weeks.
5. Hand or wrist roentgenogram changes typical of rheumatoid arthritis that must include erosions or unequivocal bony decalcification.
6. Rheumatoid nodules.
7. Serum rheumatoid factor by a method positive in less than 5% of normals.

B. Criteria for Clinical Remission in Rheumatoid Arthritis

Five or more of the following requirements must be fulfilled for at least two consecutive months:

1. Duration of morning stiffness not exceeding 15 minutes.
2. No fatigue.
3. No joint pain (by history).
4. No joint tenderness or pain on motion.
5. No soft tissue swelling in joints or tendon sheaths.
6. Erythrocyte sedimentation rate (Westergren method) less than 30 mm/hour for a female or 20 mm/hour for a male.

C. ACR Core Set of Outcome Variables

1. Tender joint count (modified Ritchie index).
2. Swollen joint count (modified Ritchie index).
3. Patient's assessment of pain (visual analog scale).
4. Patient's global assessment of disease activity (PGA).
5. Physician's global assessment of disease activity (PhGA).
6. Patient's assessment of physical function, utilizing two (2) questionnaires:
   A) The SF-36 will be completed by subjects at Day 0, Week 12, and Week 48. This questionnaire will allow us to more completely evaluate health status, quality of life, and outcome measures.
   B) The modified Clinical Health Assessment Questionnaire (mHAQ) will be completed by subjects at all study visits except Week 2. This questionnaire is more specific for the effects of rheumatoid arthritis on the activities of daily living.
7. Acute-phase reactant value (Erythrocyte Sedimentation Rate) will be collected at all study visits except Week 2.

Appendix 2: Appendix D: DAS28 Calculation

In order to calculate the DAS28, information about some disease variables is needed:

The number of swollen joints and tender joints should be assessed using 28-joint counts (tender28 and swollen28). The Erythrocyte Sedimentation Rate (ESR) should be measured (in mm/hour). In addition, the patients general health (GH) or global disease activity measured on a Visual Analogue Scale (VAS) of 100 mm (both are useable for this purpose) must be obtained.

Using this data, the DAS28 can be calculated using the following formula:

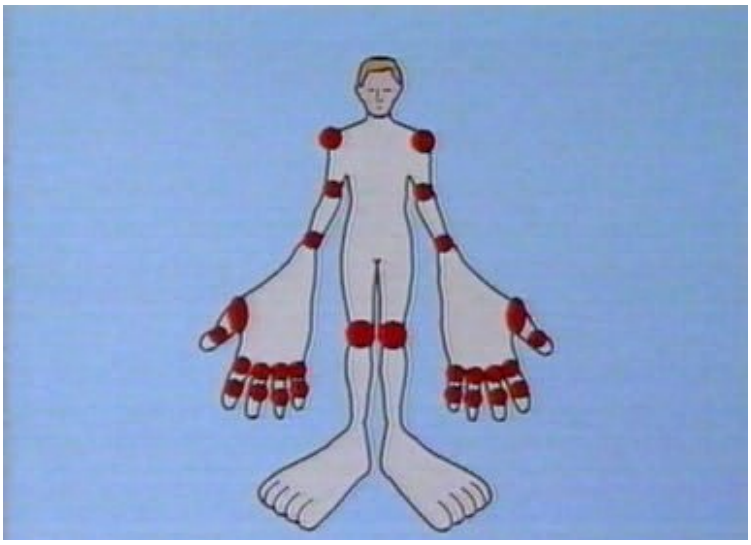
DAS28 = 0.56 * sqrt(tender28) + 0.28 * sqrt(swollen28) + 0.70 * ln(ESR) + 0.014 * GH

DAS calculators are also available online.

When no patient assessment of general health or global disease activity is present a DAS28 with 3 variables, or DAS28, can be calculated.

The DAS28 provides a number on a scale from 0 to 10 indicating the current activity of the rheumatoid arthritis of your patient. A DAS28 above 5.1 means high disease activity whereas a DAS28 below 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6 (comparable to the ARA remission criteria).

Twenty-eight tender and swollen joint scores include the same joints: shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints and the knees.



ATTACHMENT 5: ADDITIONAL BUSINESS PROPOSAL INSTRUCTIONS AND UNIFORM COST ASSUMPTIONS

Statistical and Data Coordinating Center: NIAID Immune Tolerance Network and Asthma and Allergic Diseases Cooperative Research Centers
RFP NIH-NIAID-DAIT-08-10

In addition to the format requirements for the Business Proposal that are contained in Section L of the solicitation, the information presented in this section of the RFP is intended to provide uniform cost assumptions and business clarifications.

Offerors are advised to give careful consideration to the Statement of Work, all reference material provided as attachments, the Technical Evaluation Criteria, and, the RFP as a whole, in the development of your proposal. The information requested in these instructions should be used as a guide for the development and formatting of your Business Proposal. Offerors should consider and include the information requested here, as well as **any other** information which will benefit the proposal.

BUSINESS PROPOSAL – TABLE OF CONTENTS

SECTION 1 – PROPOSAL COVER SHEET (use form NIH 2043 identified in Section J)

SECTION 2 – COST OR PRICE SUPPORT

Section L of the RFP specifies the minimum documentation requirements for cost data and all cost related support. All related documentation should be included in the proposal in a clearly marked section.

SECTION 3 – UNIFORM COST ASSUMPTIONS

1) Technical Cost Assumptions

A. IMMUNE TOLERANCE NETWORK

Assume 40 clinical trials in Phase 1, Phase II or Phase III at any given time. Patient population to include: **i**nfants, children, adolescents, and/or adults; may include special populations such as the elderly, [age greater than 65 years], pediatric populations, and/or pregnant women; Assume: 4 new trials per year of the contract, 1 new trial per year with 5 sites, 1 new trial per year with 1 site, 2 new trials per year with 15 sites. Assume: eight feasibility assessments proposal, and 4 feasibility assessments for full application.

Activity	Ongoing Activities at Contract Award (assume responsibility for)	New Work for Contract Period of Performance
1. Statistical Feasibility Assessments of Concept Proposals and Full Applications	• 3 (three) concept proposals and 1 (one) new full application] to begin protocol development within 90 days of award; • 3 (three) feasibility assessments of concept proposals and one (1) full application	• 4 (four) new clinical trials (domestic and non-domestic) each year o Assume 2 new trials per year with 15 sites each, o Assume 1 new trial per year with 5 sites, o Assume 1 new trial per year with 1 site. • 8 (eight) feasibility assessments of concept proposals • 4 (four) new full applications
2. Statistical Design and Analysis Plans	• A total of 3 (three) Phase 1/2 clinical trials in development; • A total of 7 (seven) completed Phase 1 and Phase 2 studies for which final study reports are pending and data is archived; • A total of 2 (two) active Phase 1 and 2 observational, mechanistic and surrogate / biomarker research studies; • A total of 2 (two) Phase 1 / 2 observational, mechanistic and surrogate / biomarker research studies in development; • A total of 1 (one) completed Phase 1 and 2 observational, mechanistic and surrogate / biomarker research study; • Only 20% (2/10) of the total number of mechanistic studies performed by the Network each year will require SDCC involvement.	• A total of 4 (four) new Phase I clinical trials • A total of 2 (two) new Phase II clinical trials; • A total of 1 (one) new Phase III clinical trial. • The duration of each clinical trial is as follows: o 2 clinical trials per year will be 2 years; o 2 clinical trials per year will be 4 years. • A total of 6 (six) new mechanistic studies will enter development each year. • A total of 2 (two) new biomarker research studies each year.
3. Statistical Design - Preclinical Safety Study Evaluations	• 2 active acute or chronic safety and toxicity animal studies; • 1 active chemistry, manufacturing, and controls project.	• Two (2) single dose toxicity studies (2 species/ study- Rodent and Non-rodent species) per year. • Two (2) 28-day toxicity studies (2 species/study- Rodent and Non-rodent species) per year. • Two (2) pharmacokinetic studies (2 species/study- Rodent and Non-rodent species) per year. • Two (2) safety pharmacology studies per year. • Two (2) batches of cGMP drug product for nonclinical and clinical studies per year.
4. Statistical Analysis	• Contractor to provide experienced staff to	• Contractor to provide

– Clinical Trials, Mechanistic and Surrogate/Biomarker Studies	prepare, edit, and/or maintain the following items for 21 (twenty-one) active trials including: o (i) interim statistical and trend analyses of clinical trial data for evaluating safety, toxicity, pharmacokinetics, pharmacology, efficacy, and/or exploratory endpoints; o (ii) comprehensive final statistical analyses for each trial; o (iii) statistical analyses of surrogate/biomarker studies, and o statistical designs for hypothesis-generating and hypothesis-testing mechanistic endpoints and assays.	experienced staff to prepare, edit, and/or maintain the following items for 4 (four) new trials including: o (i) interim statistical and trend analyses of clinical trial data for evaluating safety, toxicity, pharmacokinetics, pharmacology, efficacy, and/or exploratory endpoints; o (ii) comprehensive final statistical analyses for each trial; and o (iii) statistical analyses of surrogate/biomarker studies, and o statistical designs for new hypothesis-generating and hypothesis-testing mechanistic endpoints and assays.
5.Protocol Development	• Contractor staff for assigning an SDCC statistician to each network study management team responsible for protocol development and execution for ~ 21 active and enrolling clinical protocols and 3 protocols in development within 30 days of the award. • Contractor staff for protocol development and protocol writing for 5 (five) projects at the time of award including: o 3 (three) Phase 1 and 2 clinical trials in development; o 2 (two) Phase 1 and 2 observational, mechanistic and surrogate / biomarker research studies in development; o Development of protocol-related clinical trial materials for 3 (three) Phase 1 and 2 clinical trials and 2 (two) Phase 1 and 2 observational, mechanistic and surrogate / biomarker research studies in development.	• Contractor staff for assigning an SDCC statistician to each network study management team for protocol development and execution for 25 active and enrolling clinical protocols in development per year.
6. Protocol-Related Documents and Materials	• development/revisions of the study design and statistical analysis plan; • development of study-related materials including manuals of operation (MOO), investigator brochures (IBs), electronic or paper CRFs, screening and recruitment logs, and test article accountability logs. • Contractor data management staff for	• development/revisions of the study design and statistical analysis plan; • development of study-related materials including manuals of operation (MOO), investigator brochures (IBs), electronic or paper CRFs, screening and

	assisting in the preparations needed for CRF development and revisions to enable protocol-specific site monitoring visits to be conducted by the NIAID/DAIT Clinical Site Monitoring Group within 60 days of contract effective date.	recruitment logs, and test article accountability logs. • Contractor data management staff for assisting in the preparations needed for CRF development and revisions to enable protocol-specific site monitoring visits to be conducted by the NIAID/DAIT Clinical Site Monitoring Group for each year.
7. Regulatory Submissions	• the generation of tables, listings, figures, and/or summary text used for annual IND reports; • 5 **interim** clinical study reports (clinical data only) in active development at the time of award to be completed within 6 months of contract effective date; • 4 **final** clinical study reports prepared by the ITN to be reviewed and editid (clinical and mechanistic data) in active development to be completed within 6 months of the contract effective date. • 1 meeting and 1 teleconference with US or Non-US regulatory health authorities and clinical investigators within 6 months of contract effective date. • 18 clinical trials will be conducted under a US IND application held by NIAID or an industry collaborator; • 5 clinical trials will be conducted under non-domestic regulatory applications held by NIAID or an industry collaborator;	• the generation of tables, listings, figures, and/or summary text used for annual IND reports; • 4 interim clinical study reports (clinical data only) for each year; • 4 **final** clinical study reports (clinical and mechanistic data) for each year. • 5 meetings or teleconferences with US or Non-US regulatory health authorities and clinical investigators per year of the contract. • 4 (four) new IND clinical trials (domestic and non-domestic) each year; • prepare for and attend 5 (five) Pre-IND, IND, or other regulatory meetings or teleconferences with US or non-US health authorities each year of the contract.
8. Data Management and Reporting	A total of 21 active clinical trials • Data management, data quality assurance, and data analysis for 21 ongoing trials at the time of award;	• Contractor data management staff for assisting in the preparations needed for CRF development and revisions to enable protocol-specific site monitoring visits to be conducted by the NIAID/DAIT Clinical Site Monitoring Group for each year of the contract. • 1 (one) data cleaning/dataset closeout meeting of a network trial within 90 days of the award. • Web-based collection of data from all clinical trials

9. Safety Oversight and Reporting	• Contractor statistical and support staff for writing, editing, and delivering Safety Oversight Committee Reports (paper copy and electronic copy) with a summary cover memo, tables, listings, and figures for each trial under review at the time of award: o 3 (three) **pre-scheduled** meetings or teleconferences with blinded interim safety, blinded interim efficacy, and/or unblinded interim safety / efficacy reports for up to 10 protocols. o 3 (three) ***ad hoc*** blinded interim safety, blinded interim efficacy, unblinded interim safety, and/or unblinded interim safety / efficacy reports for up to 5 protocols. • Prepare and distribute 1 (one) protocol amendment for 10 active clinical trials at the contract effective date to NIAID oversight structures. • Prepare and distribute 1 (one) data and safety monitoring plan for 10 active clinical trials at the contract effective date to NIAID oversight structures. • Prepare and distribute 1 (one) interim analyses of blinded and unblinded study data including narrative studies, graphs, and figures for 10 active clinical trials at the contract effective date to NIAID oversight structures. • Contractor staff for **scheduled** and ***ad hoc*** dataset transfers (using SAS transport files) to the Network Bioinformatics Group for up to 5 protocols per month.	• Contractor statistical and support staff for writing, editing, and delivering Safety Oversight Committee Reports (paper copy and electronic copy) with a summary cover memo, tables, listings, and figures for each trial under review: o 8 (eight) **pre-scheduled** meetings and 8 (eight) pre-scheduled teleconferences with blinded interim safety, blinded interim efficacy, and/or unblinded interim safety / efficacy reports for up to 25 protocols each year. o 5 (five) ***ad hoc*** teleconferences with blinded interim safety, blinded interim efficacy, unblinded interim safety, and/or unblinded interim safety / efficacy reports for up to 10 protocols each year of the contract. • Prepare and distribute 1 (one) protocol amendment for 21 active clinical trials per year to NIAID oversight structures. • Prepare and distribute 1 (one) data and safety monitoring plan for 21 active clinical trials per year to NIAID oversight structures. • Prepare and distribute 1 (one) interim analysis of blinded and unblinded study data including narrative studies, graphs, and figures for 21 active clinical trials per year to NIAID oversight structures. • Contractor staff for **scheduled** and ***ad hoc*** dataset transfers (using SAS transport files) to the Network Bioinformatics Group for up to 5 protocols per month per year.
10. Clinical Study Internet-based Collaboration Portal	• Establish, maintain and update one internet-based collaboration portal to house clinical trial information and study-specific documents and materials within 60 days from time of award. This collaboration portal will contain a dedicated page for each clinical trial, and will have a total of ~ 500 users for	• Contractor staff to maintain an SDCC collaboration portal for each year and interface with 3 (three) active network-sponsored and maintained sites including

	all 3 (three) active sites requiring access to various pages at any time. • Contractor staff for weekly interface with 3 active network-sponsored and maintained clinical trial-specific collaboration portals involving 4K web pages per site including: o **Enrollment Data/Reports:** http://datacenter.immunetolerance.org o **Network Members Website for New Proposals and Meetings:** http://www.immunetolerance.org/resources/meeting.html o **Protocol Documents:** https://documents.immunetolerance.org/docushare/dsweb/HomePage	o **Enrollment Data/Reports:** http://datacenter.immunetolerance.org o **Network Members Website for New Proposals and Meetings:** http://www.immunetolerance.org/resources/meeting.html o **Protocol Documents:** https://documents.immunetolerance.org/docushare/dsweb/HomePage
11. Study Communication, Collaboration, and Reporting	• Prepare and participate in a clinical site training visit to 10 domestic clinical sites and 5 foreign clinical sites. 3 Contractor staff members to participate in each training visit of 2 days in duration. Assist in the assessment of site compliance with randomization instructions and appropriate administration of study drug(s) test articles.	• Prepare and participate in a clinical site training visit to ~20 domestic clinical sites and ~10 foreign clinical sites per year. 3 Contractor staff members to participate in each training visit of ~ 2 days in duration. Assist in the assessment of site compliance with randomization instructions and appropriate administration of study drug(s) test articles.
12. Clinical Site Training, Assessment, and Technical Assistance	• 2 (two) contract staff to prepare and participate in 10 site assessments per year, duration of 2 days to include 6 domestic clinical sites and 4 foreign sites; • 10 webcasts dedicated to electronic data entry and remote data capture will be needed within 90 days of the time of award; • 2 meetings dedicated to electronic data entry and remote data capture will be needed within 90 days of the time of award; • 2 meetings for GCP training will be needed within 90 days of the time of award.	• 2 (two) contract staff to prepare and participate in 10 site assessments per year, for a duration of 2 days, to include 6 domestic clinical sites and 4 foreign sites; • 25 webcasts/year dedicated to electronic data entry and remote data capture; • 10 meetings/year dedicated to electronic data entry and remote data capture; • 5 meetings per year for GCP training • 3 meetings per year for data cleaning and dataset closeouts of network trials.

B. ASTHMA AND ALLERGIC DISEASES COOPERATIVE RESEARCH CENTERS

Activity	Ongoing Activities at Contract Award (assume responsibility for)	New Work for Contract Period of Performance
1. Statistical Feasibility Assessments of Concept Proposals	• A total of 1 (one) clinical research protocol	• (two) concept proposals per year.
2. Statistical Design and Analysis Plans	• A total of 5 (five) active and enrolling clinical research protocols • 5 protocols in development within 30 days of contract effective date.	• A total of 10 (ten) active and enrolling clinical research protocols • 1 protocol in development each year.
3. Statistical Analysis and Final Study Reports	• A total of 5 (five) active and enrolling clinical research protocols • 1 (one) protocol in development within 30 days of contract effective date.	• A total of 3 clinical research protocols per year; 1 requiring interim statistical analysis and all 3 requiring final statistical analysis

2) Meetings and Travel

A. IMMUNE TOLERANCE NETWORK

1. ITN Scientific / Business Meetings	• three (3) 2 -day Network Steering Committee meetings per year, one located on the east coast, one located on the west coast and one in the Midwest for no more than four (4) participants. • two (2) 2-day business meetings with NIAID and Network staff per year, conducted on an as needed basis, located in the USA for no more than five contractor (5) participants. • two (2) 2-day meetings for non-local scientific/medical professional development per year for three (3) contractor participants.	• three (3) 2 -day Network Steering Committee meetings per year, one located on the east coast, one located on the west coast and one in the Midwest for no more than four (4) participants. • two (2) 2-day business meetings with NIAID and Network staff per year, conducted on an as needed basis, located in the USA for no more than five contractor (5) participants. • two (2) 2-day meetings for non-local scientific/medical professional development per year for three (3) contractor participants.
2. Contract Initiation	• 1 meeting in Bethesda, Maryland	• 1 meeting in Bethesda, Maryland within 10

Meeting	within 10 calendar days after effective date of contract; 2-night stay with attendance by all of the contractor's key personnel.	calendar days after effective date of contract; 2-night stay with attendance by all of the contractor's key personnel.
3. Site Assessments	• 10 two-day site assessments per year conducted by 2 contractor staff: o 6 domestic clinical sites o 4 foreign clinical sites	• 10 two-day site assessments per year conducted by 2 contractor staff: o 6 domestic clinical sites o 4 foreign clinical sites
4. Protocol Development Meetings	• ten (10) 1-day face-to-face protocol development meetings per year, including five on the east coast, two on the west coast and three in the Midwest for four (4) contractor participants.	• ten (10) 1-day face-to-face protocol development meetings per year, including five on the east coast, two on the west coast and three in the Midwest for four (4) contractor participants.
5. Clinical Trial - Investigator Meetings	• 4 (four) contractor staff to participate and prepare for a 2-day Investigator Meeting for ~ 4 new clinical trials at contract effective date. o 3 (three) of these investigator meetings will be located within the USA and one will be located outside the USA. • Study Closeout Meetings - Up to 3 (three) contractor staff to attend a 2-day Study Closeout Meeting for ~ 4 clinical trials closing each year of the contract as requested by the Project Officer.	• 4 (four) contractor staff to participate and prepare for a 2-day Clinical Trial Investigator Initiation Meeting for ~ 4 new clinical trials per year as requested by the Project Officer. o Three of these investigator meetings will be located within the USA and one will be located outside the USA. • Interim Investigator Meetings - 3 (three) contractor staff to attend a 2-day Interim Investigator Meeting for 4 ongoing clinical trials per year as requested by the Project Officer. • Study Closeout Meetings - 3 (three) contractor staff to attend a 2-day Study Closeout Meeting for 4 clinical trials closing each year as requested by the Project Officer.
6. Clinical Site Training Visits	• 2 (two) contractor staff to participate in planning and conducting a clinical site training visit to 10 domestic clinical sites and 5 foreign clinical sites. Each training visit will be 2 days in duration. • 2 contractor staff to participate in weekly clinical site training webcasts, videocasts and teleconferences for 10 clinical trials.	• Up to 2 (two) contractor staff to participate in planning and conducting a clinical site training visit to ~10 domestic clinical sites and/or ~5 foreign clinical sites per year as requested by the Project Officer. Each training visit will be 2 days in duration. • 2 contractor staff to participate in weekly clinical site training webcasts, videocasts and teleconferences for 20 clinical trials.
7. Regulatory Health Authority Pre-IND or IND meetings.	• 5 meetings or teleconferences with US regulatory health authorities and clinical investigators within 6 months of contract effective date. • 5 (five) 1 (one) day meetings will be held in Bethesda, MD with 3 (three) contractor participants.	• 10 (ten) meetings or teleconferences with US regulatory health authorities and clinical investigators per year. • 10 (ten) 1 (one) day meetings will be held in Bethesda, MD with 3 (three) contractor participants.

B. ASTHMA AND ALLERGIC DISEASES COOPERATIVE RESEARCH CENTERS

No special meetings and travel requirements for AADCRCs

3) Special Shipping and Packaging

No special shipping and packaging requirements.

4) Storage

No storage requirements.

5) Government Furnished Equipment (GFE)

☒ Government Furnished Equipment available to be transferred from incumbent contractor.

If this initiative is a recompetition, the Contract Specialist will provide a listing of all Government Furnished Equipment that has been purchased under the incumbent contract with contract funds. The CS will include this listing as an attachment to the RFP and potential offerors will be advised that this equipment is available to be transferred to the successful offeror.

☐ The purchase of Government Furnished Equipment will not be authorized as a direct charge under this contract.

SECTION 4 – OPTIONS

Option 1: Extension of Base Period of Performance

Provide in the Budget Proposal a separate breakdown of proposed cost to continue the services provided for in the base period for both the ITN and the AADCRCs for one additional year.

Option 2: Provision of Additional SDCC Support Services for the NIAID Asthma and Allergic Diseases Cooperative Research Centers (AADCRCs)

Provide a budget proposal based on the full range of data collection, storage, management, quality control and reporting services, as specified in Part D of the Statement of Work, Option 2, for a Phase I clinical trial of an experimental product to be conducted at 2 study sites for a total of 40 study participants.

Option 3: Provision of SDCC Support Services for Additional DAIT Clinical Trial Programs and Projects

Provide a budget proposal based on the full range of SDCC services, as specified in Part A of the Statement of Work, for a Phase II clinical trial of an experimental product to be conducted at 5 study sites for a total of 150 study participants. Assume a 3-year enrollment period and a total study duration of 6 years.

SECTION 5 - TABLE OF CONTENTS FOR DOCUMENTATION REQUIRED UNDER SECTION L OF THE SOLICITATION

1) Small Business Subcontracting Plan

Section L of the RFP specifies the minimum documentation requirements for completing a subcontracting plan. This plan should be turned in with the original proposal. All related documentation should be included in the proposal in a clearly marked section.

2) Extent of Small Disadvantaged Business Participation

Section L of the RFP specifies the minimum documentation requirements for small disadvantaged business utilization. This information should be turned in with the original proposal. All related documentation should be included in the proposal in a clearly marked section.

3) Past Performance Data, including references

Section L of the RFP specifies the minimum documentation requirements for providing past performance information. This information should be turned in with the original proposal. All related documentation should be included in the proposal in a clearly marked section.

ATTACHMENT 6: ADDITIONAL RFP MATERIALS

Statistical and Data Coordinating Center (SDCC):
NIAID Immune Tolerance Network and
Asthma and Allergic Diseases Cooperative Research Centers

RFP-NIH-NIAID-DAIT-08-10

☒ The RFP-Specific Materials below are applicable to this solicitation.

These additional RFP materials provide supplemental information for potential offerors on various activities of the clinical research programs and clinical research services contracts supported by the NIAID Division of Allergy, Immunology and Transplantation (DAIT). Included in these additional RFP materials are the following:

1. A list of Immune Tolerance Network (ITN) laboratories
2. A table of ITN clinical trials and assay studies (in development, active and closed to enrollment)
3. A list of the Asthma and Allergic Diseases Cooperative Research Centers (AADCRCs)
4. A table of AADCRC clinical trials and mechanistic studies in development
5. Descriptions of DAIT-funded clinical research support services contracts
6. Descriptions of NIH-funded clinical research programs supported in full or in part by DAIT

Additional information on the ITN organizational structure, ITN-supported investigators and procedures for the submission of proposals can be found on the ITN website (www.immunetolerance.org).

1. IMMUNE TOLERANCE NETWORK LABORATORIES

DNA-based Assays:

HLA-Typing Core
Director: Lee Ann Baxter-Lowe, University of California San Francisco

RNA-based Assays (Gene expression profiling):

High Throughput Real Time PCR Core
Director: TBD

RNA Preparation Core
Directors: Paul Wood, University of Pittsburgh;

Microarray
Directors: Steve McPhail, Expression Analysis

Protein & Cellular Assays:

Enzyme-linked Immunospot (ELISPOT) Assay Core
Directors: TBD

MHC-Peptide Tetramer Facility
Directors: Gerald Nepom, Virginia Mason Research Center, Seattle, WA; Jeffrey A. Bluestone, University of California San Francisco, San Francisco, CA

Type 1 Diabetes Autoantibody Facility
Director: George Eisenbarth, University of Colorado Health Science Center, Denver, CO

Flow Cytometry Core, United States
Director: Paul Wallace, Roswell Park Cancer Institute
Director: Wade Bolton, Beckman Coulter, Inc.

Flow Cytometry Core, Europe
Director: Peter Trinder, Thymed GmbH, Mainz, Germany

Alloantibody & Flow Cross-match Core
Director: Robert Bray, Emory University, Atlanta, GA

IDO Core
Director: David Munn, Medical College of GA, GA

AlloELISPOT Core
Director: TBD

Luminex Core
Director: Ger T. Rijkers, Wilhelmina Children's Hospital, Utrecht, Netherlands

Trans-vivo Delayed Type Hypersensitivity Core
Director: Will Burlingham, University of Wisconsin, Madison, WI

ELISA Core
*Director: R*obert Hamilton, Johns Hopkins Allergy and Asthma Center, Baltimore, MD

Tissue & Histochemical Assays:

Liver Tissue Analysis Core
Director: Anthony Demetris, University of Pittsburgh

Renal Pathology Core
Director: Robert Colvin, Harvard University

Additional Cores:

CMV/EBV Viral Load Core
Contractors: ViraCor, Lee's Summit, MO

Central Cell Processing Core facility
Director: David Toke, Rutgers University Cell and DNA Repository

Specimen Support:

Clinical Specimen Repository
Contractors: Fisher Biosciences, Rockville MD

Data Support:

Bioinformatics/Data Analysis Core
Director: Dave Parrish, Immune Tolerance Network
Director: Vicki Seyfert, Immune Tolerance Network

2. ITN CLINICAL TRIALS AND ASSAY STUDIES

Area of Study	Protocol Number	Protocol Name	Target Enrollment / # of Sites	Protocol Status (PSD=Projected Start Date)	Study Completion	Protocol Chair(s)
DIABETES	ITN018AI	A Pilot Study to Evaluate the Safety of Interleukin-2 (IL-2) and Sirolimus (Rapamycin) Combination Therapy In Recent-Onset Type 1 Diabetes Mellitus	10/1	PROTOCOL DEVELOPMENT PSD: 04/07	JUL 2009	C. GREENBAUM, MD
DIABETES	ITN028AI	Thymoglobulin for New Onset T1DM	78/6	PROTOCOL DEVELOPMENT PSD: 04/07	OCT 2009	S.GITELMAN, MD
DIABETES	TBD	Auto-Antigen Vaccination for New Onset T1DM	TBD	PROTOCOL DEVELOPMENT PSD: FALL 2007	TBD	T. ORBAN, MD
RHEUMATOLOGY	ITN034AI	Treatment of Systemic Lupus Erythematosus	TBD	PROTOCOL DEVELOPMENT PSD: TBD	TBD	B. DIAMOND, MD; D. WOFSY, MD
MULTIPLE SCLEROSIS	ITN035AI	Use of Orencia® in RRMS	120/TBD	PROTOCOL DEVELOPMENT PSD: TBD	TBD	S. KHOURY, MD
TRANSPLANT LIVER	ITN029ST	IS Withdrawal in Stable Pediatric LD Liver Tx Recipients	20/2	PROTOCOL DEVELOPMEN PSD: 06/07	OCT 2012	S. FENG, MD
DIABETES	ITN017AI	Evaluation of Tolerability, Safety and Pharmacokinetics of hOKT3γ1 (Ala-Ala) in Participants with Type 1 Diabetes Mellitus	12/2	CLOSED TO ENROLLMENT	DEC 2008	K. HEROLD, MD
DIABETES	ITN012AI	Auto-antigen Vaccination for New Onset T1DM	12/1	CLOSED TO ENROLLMENT	MAR 2007	T. ORBAN, MD
TRANSPLANT LIVER	ITN024ST	Immunosuppression Withdrawal in Liver Transplant Recipients	211/14	CLOSED TO ENROLLMENT	MAR 2007	R. THISTLETHWAITE, MD
TRANSPLANT KIDNEY/ BMT	ITN008ST	Combined HLA-Matched Bone Marrow and Kidney Transplantation for Multiple Myeloma with Renal Failure	10/1	CLOSED TO ENROLLMENT	DEC 2006	M. SYKES, MD; A. COSIMI, MD
DIABETES	ITN027AI	New Phase II Multiple Dose Treatment of T1DM with hOKT3γ1	81/6	VOLUNTARY HOLD	TBD	K. HEROLD, MD
TRANSPLANT ISLET	ITN015CT	Evaluation of the Tolerogenic Efficacy of hOKT3γ1 and Sirolimus Immunotherapy in T1DM	12/1	VOLUNTARY HOLD	TBD	B. HERING, MD
ALLERGY	ITN032AD	A Trial of Oral Tolerance Induction for Prevention of Peanut Allergy	440/2	ACTIVE START DATE: 12/06	JAN 2001	G. LACK, MD
RHEUMATOLOGY	ITN021AI	Rituximab Therapy for the Induction of Remission and Tolerance in ANCA-Associated Vasculitis	200/9	ACTIVE START DATE 12/04	DEC 2009	U. SPECKS, MD
MULTIPLE SCLEROSIS	ITN020AI	A Randomized, Double-Blind, Placebo Controlled, Multi-Center Study to Evaluate the Efficacy and Safety of Atorvastatin in Patients with Clinically Isolated Syndrome and High Risk of Conversion to MS	152/14	ACTIVE START DATE: 12/05	DEC 2010	S. ZAMVIL, MD

TRANSPLANT KIDNEY	ITN013ST	The Use of Campath-1H, Tacrolimus and Sirolimus Followed by Sirolimus Withdrawal in Renal Transplant	10/1	ACTIVE START DATE: 2/04	FEB 2008	S.KNECHTLE, MD
TRANSPLANT KIDNEY	ITN010ST	Renal Allograft Tolerance Through Mixed Meal Chimerism	10/1	ACTIVE START DATE: 05/02	2010	D. SACHS, MD B. COSIMI, MD
TRANSPLANT LIVER	ITN030ST	IS Withdrawal in Liver Tx Recipients with HCV Infection	157/2	ACTIVE START DATE: 10/05	AUG. 2011	A. SHAKED, MD
ASTHMA	ITN025AD	Prophylaxis of Atopy and Asthma in Children	200/5	ACTIVE START DATE: 10/05	DEC 2010	P. HOLT, DSC
TRANSPLANT KIDNEY	ITN023ST	LEA29Y in an Immunosuppression Withdrawal Regimen in Recipients of Non-HLA Identical Living Donor Renal Transplants	30/2	ACTIVE START DATE: 01/07	NOV 2009	F. VINCENTI, MD
ITN Assay						
ASSAY	ITN506AS	Monitoring of CMV-Specific T-Cells Following Tolerance Induction Protocols	0/0	PROTOCOL DEVELOPMENT PSD: TBD	TBD	F. KERN, MD
DIABETES	ITN504AI	Cytokine Production in Children with Pre-Clinical and Clinical T1DM	210	ACTIVE	TBD	J. IIONEN, MD
MULTIPLE SCLEROSIS	ITN510AI	Ex-vivo Detection of Co-stimulation dependent Myelin Antigen-mediated T-cell Responses to Relapsing Remitting Multiple Sclerosis Patients and Normal Healthy Controls	40	ACTIVE	TBD	J. KREIGER, PHD
TRANSPLANT KIDNEY	ITN50ST	Identification and Mechanistic Investigations of Tolerant Kidney Transplant Patients	260	ACTIVE	TBD	K. NEWELL, MD/PHD

3. ASTHMA AND ALLERGIC DISEASES COOPERATIVE RESEARCH CENTERS

DAIT supports 15 Asthma and Allergic Diseases Cooperative Research Centers (AADCRCs).

PI Name	Institution	Title
KHURANA HERSHEY, GURJIT K	CHILDREN'S HOSPITAL MED CTR (CINCINNATI)	Epithelial Genes In Allergic Inflammation
MACGLASHAN, DONALD W	JOHNS HOPKINS UNIVERSITY	Efficacy of IgE in Mediating Allergic Reactions in Vivo
PLATTS-MILLS, THOMAS A.	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE	Asthma and Allergic Disease Center
BASEMAN, JOEL B	UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANT	Role of unique ADP-ribosylating vacuolating Mycoplasma pneumoniae toxin in asthma
KAPLAN, MARK H.	INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS	Pathogenesis of Atopic Dermatitis
NEL, ANDRE E.	UNIVERSITY OF CALIFORNIA LOS ANGELES	Xenobiotics, Oxidative Stress and Allergic Inflammation
HOLTZMAN, MICHAEL JAY	WASHINGTON UNIVERSITY	Innate and Adaptive Immune Signaling in Asthma
GERN, JAMES E.	UNIVERSITY OF WISCONSIN MADISON	Mechanisms of Rhinovirus-Induced Exacerbations of Asthma
BROIDE, DAVID H	UNIVERSITY OF CALIFORNIA SAN DIEGO	Airway Inflammation and Airway Remodeling
EISSA, TONY	BAYLOR COLLEGE OF MEDICINE	Innate Immunity in Allergic Airway Inflammation Asthma
LIU, YONG-JUN	UNIVERSITY OF TEXAS MD ANDERSON CAN CTR	Asthma and Allergic Diseases Cooperative Research Center
SOLWAY, JULIAN	UNIVERSITY OF CHICAGO	Molecular Mechanisms of Asthma
GEHA, RAIF S	CHILDREN'S HOSPITAL BOSTON	Molecular Mechanisms of the IgE Allergic Response
AUSTEN, FRANK	BRIGHAM AND WOMEN'S HOSPITAL	Cellular Basis of Hypersensitivity Diseases in Humans
SAMPSON, HUGH	MOUNT SINAI SCHOOL OF MEDICINE OF NYU	Immunologic Basis of Cow Milk Induced Hypersensitvities

4. AADCRC CLINICAL TRIALS AND MECHANISTIC STUIDES IN DEVELOPMENT

AREA of STUDY	**Protocol # and U19 Grant #**	**Protocol Name**	**Target Enrollment/ # of sites**	**Protocol Status** (PSD=Projected Start Date)	**Study Completion**	**PROTOCOL CHAIR(S)**
Allergy	**AADCRC 1 U19AI070345**	Xolair Impact on Nasal Provocation Challenge	**50**	Protocol Development PSD: TBD	TBD	B. Bochner
Allergy	**AADCRC 2 U19AI070345**	Xolair Impact on Cat Allergen Challenge	**30**	Protocol Development PSD: TBD	TBD	B. Bochner
Allergy	**AADCRC 3 U19AI070345**	Xolair Impact on Food Allergy Challenge	**30**	Protocol Development PSD: TBD	TBD	B. Bochner
Allergy	**AADCRC 4 U19AI070345**	Xolair Impact on Lower Airway Segmental Allergen Challenge	**20**	Protocol Development PSD: TBD	TBD	J. Schroeder
Allergy	**AADCRC 5 U19AI070453**	SFN Impact on DEP Nasal Challenge	**40**	Protocol Development PSD: TBD	TBD	M. Reidel
Allergy	**AADCRC 6 U19AI070453**	SFN Impact on Allerlgen and DEP Challenge	**40**	Protocol Development PSD: TBD	TBD	A. Saxon
Allergy	**AADCRC 7 U19AI070453**	SFN Impact on DEP and KLH Nasal Challenge	**40**	Protocol Development PSD: TBD	TBD	A. Saxon
Asthma	**AADCRC 8 U19AI070503**	Immunologic Response to Artificially-Induced Rhinovirus Infection	**300**	Protocol Development PSD: TBD	TBD	J. Gern
Asthma	**AADCRC 9 U19AI070364**	Impact of Xolair on Artificially-Induced Rhinovirus Infection Among Asthmatics	**30**	Protocol Development PSD: TBD	TBD	J. Woodfolk.
Allergy	**AADCRC 10 P01 AI044236 (To be converted to a U19 Grant.)**	Oral Immunotherapy with Milk, in Combination with Omalizumab.	**TBD**	Protocol Development PSD: TBD	TBD	H. Sampson

5. DAIT-FUNDED CLINICAL RESEARCH SUPPORT SERVICES CONTRACTS

DAIT Regulatory Management Center

Social & Scientific Systems, located in Silver Spring, MD, provides support services for regulatory and clinical compliance functions and requirements associated with Health Authority Applications such as Investigational New Drug (IND) Applications and Amendments as described below [http://www.niaid.nih.gov/contract/archive/rfp0444.pdf]. This includes the following:

1. Technical assistance for regulatory and current Good Clinical Practice (cGCP) compliance;
2. Electronic tracking of IND safety reports;
3. Electronic clinical site registration system;
4. General administrative support for regulatory affairs and cGCP compliance; and
5. Logistical support for all DAIT-sponsored clinical trials.

DAIT Clinical Site Monitoring Group

PPD Development, LP located in Wilmington, NC, provides evaluations of good clinical research practices, regulatory compliance, accurate protocol implementation, international quality assurances, and test agent accountability during periodic on-site visits to all DAIT-funded clinical trial sites. Specific responsibilities of the PPD Development contract include, but are not limited to, the following [http://www.niaid.nih.gov/contract/archive/rfp0446.pdf]:

1. Examine source documents to assess accuracy and completeness of trial data;
2. Identify problems with protocol implementation, adherence to GCP and all applicable regulatory requirements;
3. Verify proper storage, dispensing and accountability of investigational study products;
4. Provide training on general protocol conduct, cGCP, quality management, and DAIT procedures;
5. Review internal quality assurance/quality control plans; and
6. Report progress during the contract and file ending reports that are comprehensive and specific to the description and time tables set forth in the contract.

DAIT Drug Distribution Center

EMINENT Services Corporation, located in Frederick, MD, establishes and maintains the Clinical Products Distribution Center for the purpose of purchasing, dispensing and providing quality control of study products. Specific responsibilities of the Contractor include, but are not limited to, the following:[http://www.emiserv.com].

1. Purchasing, receiving, storing, labeling, packaging, shipping and distribution of study products;
2. Inventory control and quality assurance of study supplies for each protocol;
3. Pharmaceutical services including written reviews, reports, transfers, packaging, storage, dosage, labeling, usage and returns of products in conjunction with the NIAID Project Officer's approval while establishing a secure clinical web site for clinical site pharmacists that supplies protocol-specific information and requirements;
4. Security/safety measures and procedures;
5. Processing and disposal of returned and unused drug product; and
6. Record maintenance.

DAIT Coordinating Center for Biostatistics, Data Management and Pharmacovigilance

PPD Development, LP, located in Wilmington, NC, provides a resource to the ITN to assure efficient clinical study design, conduct, safety monitoring and data analysis.

Current data management tools provided by PPD include Data Oracle Clinical Database V4.5.1, Oracle Clinical RDC V 4.5.1 and Oracle Thesaurus Management System 4.5.2. The Data Oracle Clinical Database manages data collected during trials, provides study layout and design features, allows for data accuracy checks and handles data tracking, as well as analysis and reporting. PPD uses Oracle Clinical RDC for electronic remote data capture and query management/resolution. The last data management program allows coding of various AE and medical data terms into groupings for easier statistical evaluations.

SAS V 8.2 serves as a primary biostatistical tool. The program provides a comprehensive and integrated platform for exploratory data analysis. It can create data tables, listings and figures to support safety reviews. SAS also has easy transport and reformatting capabilities, making information distribution between groups easier.

Oracle AERS (adverse event reporting system) controls a comprehensive database for SAE tracking and reporting. All data entry for each event enters the system through a CRO, which also manages the servers, databases and software.

Responsibilities of the Contractor include, but are not limited to, the following [http://www.niaid.nih.gov/contract/archive/rfp0459.pdf]:

1. Providing statistical leadership and clinical trial design expertise for the development of protocols and analysis of study data;
2. Establishing and administering data collection, management, quality assurance and reporting systems;
3. Establishing and managing a safety reporting center;
4. Detailed record maintenance and timely reporting; and

5. Collaboration with DAIT and research groups.

DAIT Bioinformatics Integration Support Contract (BISC)

Northrop Grumman Information Technology, located in Rockville, MD, provides information technology support in the production, analysis, archiving, exchange and integration of genomic, proteomic and related data to DAIT-funded research programs via the Immunology and Data Analysis Portal (ImmPort at http://www.immport.org/index.html). Specific responsibilities of the Contractor include, but are not limited, to the following:

1. Accelerate a more collaborative and coordinated research environment;
2. Create an integrated database that broadens the usefulness of scientific data and advances hypothesis-driven and hypothesis-generating research;
3. Integrate relevant data sets from participating laboratories, public and government databases, and private data sources; and
4. Provide analysis tools to advance immunological research

6. NIH-FUNDED CLINICAL RESEARCH PROGRAMS

The Autoimmune Centers of Excellence (ACEs)

Nine Autoimmunity Centers of Excellence (ACEs) conduct collaborative basic and clinical research on autoimmune diseases, including single-site and multi-site pilot clinical trials of immunomodulatory therapies and mechanism-of-action studies. The ACEs support close interaction between clinicians and basic researchers, which should facilitate the identification of effective tolerance induction and immune modulation strategies to treat or prevent disease, and accelerate the translation of scientific advances to the clinic. Examples of ACEs-supported clinical trials include: anti-CD20 for systemic lupus erythematosus; sirolimus for multiple sclerosis; and a double-masked study of the combination of copaxone and albuterol versus copaxone alone for multiple sclerosis. The ACEs are co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIH Office of Research on Women's Health.

The Clinical Trials in Organ Transplantation (CTOT)

In FY 2004, NIAID, in collaboration with the NIDDK and the National Heart, Lung and Blood Institute (NHLBI), established a clinical consortium to improve the success of organ transplants. The goals of the consortium are to identify genetic factors in patients that could help doctors predict transplant outcomes as well as responses to post-transplant therapy; develop diagnostic tests that enable early detection and ongoing monitoring of immune-related processes; and test the safety and effectiveness of new, less toxic immunosuppressive drugs. The consortium is comprised of three institutions: Brigham and Women's Hospital, Boston; Cleveland

Clinic Lerner College of Medicine of Case Western Reserve University; and the University of Pennsylvania, Philadelphia.

Diabetes TrialNet

TrialNet is an international network of investigators, clinical centers, and core support facilities dedicated to the development and implementation of clinical trials of agents to slow the progression of type 1 diabetes in new onset patients and to prevent the disease in at-risk patients. The network also supports natural history studies to provide information on risk factors associated with development of type 1 diabetes and to inform the design of future trials. TrialNet is supported by the NIDDK, NIAID, the National Institute of Child Health and Human Development (NICHD), and the Juvenile Diabetes Research Foundation International (JDRF).

The Environmental Determinants of Diabetes in the Young (TEDDY)

TEDDY is an international consortium to recruit genetically-susceptible newborns for studies to test the role of infectious agents, dietary factors, and other environmental conditions that may trigger type 1 diabetes. Funded by the NIDDK, NIAID, NICHD, the National Institute of Environmental Health Sciences (NIEHS), CDC, and the JDRF, this long-term project will follow participating individuals through adolescence to ascertain the onset of autoimmunity and/or type 1 diabetes.

Consortium for Food Allergy Research (CoFAR)

CoFAR was established to conduct multi-center clinical trials, observational studies, mechanistic studies and basic research towards further understanding of the best possible treatment approaches for food allergies. CoFAR is supported through a DAIT grant to Dr. Hugh Sampson, Mount Sinai Medical Center, and to The EMMES Corporation. Mount Sinai is the Lead Clinical Center and EMMES serves as the Statistical and Clinical Coordinating Center (SACCC) for the research program.

Centers for Medical Countermeasures Against Radiation Program (CMCR)

This program seeks to expand the medical options available to triage, prevent and/or treat radiation-induced injury and minimize terrorist threats. The NIAID established eight Centers for Medical Countermeasures against Radiation (CMCRs) in September 2005. The Centers include Columbia University, Dana Farber Cancer Institute, Duke University, Fred Hutchinson Cancer Research Center, Medical College of Wisconsin, University of California, Los Angeles, University of Pittsburgh, and the University of Rochester medical Center.

Cooperative Clinical Trials in Pediatric Transplantation (CCTPT)

The CCTPT is a cooperative research program sponsored by both NIAID and private industry. Study objectives are the development of pre, peri, and post transplant

therapy and immunomodulatory interventions to induce long-lived graft function with and without temporary or permanent withdrawal of immunosuppression. Improvements will facilitate growth and development in pediatric renal graft recipients.

Clinical Islet Transplantation (CIT) Consortium

The CIT Consortium is a network of clinical centers and a data coordinating center established in 2004 to conduct studies of islet transplantation in patients with type 1 diabetes. Studies conducted by the CIT Consortium focus on improving the safety and long-term success of methods for transplanting islets, the insulin-producing cells of the pancreas, in people whose own islets have been destroyed by the autoimmune process that characterizes type 1 diabetes. The network includes the following centers: University of Miami, Miami, Florida; University of Minnesota, Minneapolis, Minnesota; University of Pennsylvania, Philadelphia, Pennsylvania; Emory University, Atlanta, Georgia; Northwestern University, Chicago, Illinois; University of Alberta, Edmonton, Alberta, Canada; Uppsala University, Uppsala, Sweden; and Karolinska University, Stockholm, Sweden.

Inner-City Asthma Consortium (ICAC)

The ICAC program carries out a long-range scientific plan to reduce asthma severity and prevent asthma among children in U.S. inner cities, and continues to develop and implement a number of clinical trials. Additionally, the NIAID hopes to identify the mechanisms involved in the immunopathogenesis of asthma in these populations.

Atopic Dermatitis and Vaccinia Network (ADVN)

The NIH has launched a five-year program of clinical studies related to atopic dermatitis (also known as eczema). The Atopic Dermatitis and Vaccinia Network (ADVN) is a consortium of academic medical centers that conduct clinical research studies in an attempt to make smallpox vaccines safer for millions of people with atopic dermatitis.

Hematopoietic Stem Cell Transplantation (HSCT)

In 1999, NIAID awarded 3 contracts for the creation of a consortium to study hematopoietic stem cell transplantation (HSCT) for the treatment of autoimmune diseases. The contracts resulted in the development of 3 clinical protocols by 3 distinct clinical trial groups using high dose immunosuppressive therapy (HDIT), followed by HSCT for the treatment of Severe Systemic Sclerosis (SSc), Systemic Lupus Erythematosus (SLE), and Multiple Sclerosis (MS). In addition to clinical outcomes, mechanisms of disease, remission and relapse will be evaluated as part of all three studies. The SSc and SLE trials consist of two treatment arms (an active control regimen and a transplant regimen). The SSC trial is a phase II/III pivotal trial evaluating safety and clinical success in subjects with severe, rapidly progressive

systemic sclerosis. The SLE trial (phase II) evaluates safety of HSCT in subjects with severe, steroid dependent SLE. The phase II single arm MS trial focuses on safety and the assessment of biological activity using MRI measures and clinical outcomes.